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Enclosures:

(a) Photocopies of all bibliographic references except those marked with (*) to be forwarded at a later date; those marked with (#) were forwarded with earlier chapters and marked in the Cumulative Index.

(b) Photocopies of 44 foreign articles not cited in the text.

(c) Titles of 78 foreign articles not cited in the text.

(d) Titles of 54 English articles not cited in the text.

(e) Photocopies of 5 Spanish articles and 10 Spanish titles not cited in the text.

(f) Medline printout of publications by Enrique Najero, M.D.

(g) Publications by Roffo 1910 to 1935 from Index to the Literature of Experimental Cancer Research, Donner Foundation [pages 995 to 996 were used in Harris' ERR, page 35; note that tobacco titles end on page 995]

III. THE 1930's. IMPACT OF FOREIGN STUDIES ON AMERICAN CONCEPTS OF CARCINOGENESIS

The thread of connection between literature of the 1920's and that of the 1930's is the 1928 quotation of Greenwood that a "man of the highest order of ability" was needed to properly apply epidemiology to identify cancer causation (see page 117). Major Greenwood subsequently wrote a monograph entitled Epidemics and Crowd Diseases (3501) which essentially outlined the pitfalls of statistics. Half a century later, his peers considered Greenwood's monograph as a milestone in the field of epidemiology that has attracted scientists of "the highest order of ability." Since Greenwood was from England, he attracted followers from Great Britain and the British Empire. The Americans were independently starting Schools of Public Health at Baltimore, Philadelphia, New York City and Boston that differed in philosophy from European schools. The fundamental difference related to whether public health agencies should not only control infectious diseases (by improving water supply, sewer system and food distribution), but also influence human behavior and personal habits. With this as a background, it is not surprising to discover that during the 1930's, American scientists interested in lung cancer had a different research approach from European, Japanese, and South American scientists.

Harris' State of the Art Report

According to Harris, the tobacco companies should have conducted research on tobacco and lung cancer during the 1930's based on the following interpretation of literature during that decade:

"9.1. During the early 1930s-- and unquestionably by no later than the late 1930s-- a reasonably prudent manufacturer of cigarettes should have been conducting or sponsoring careful, sustained scientific research into the potentially cancer-causing effects of its products.

9.2. Among the methods of scientific research available by the late 1930s, a reasonably prudent manufacturer of cigarettes could have employed the following: controlled, detailed clinical or epidemiological studies on smoking habits among cancer patients and comparison subjects; detailed chemical analyses of potentially carcinogenic compounds in cigarette smoke and smoke components; and controlled, long-term experimental carcinogenicity studies in various laboratory animals exposed to whole cigarette smoke or smoke components.

9.3. During the 1920s and 1930s, cancer research was supported mainly by private charitable foundations. Not until after World War II was there substantial government funding for cancer research grants (Triolo and Shimkin 1969; Shimkin 1977). The relative lack of research funds through the late 1930s enhanced the obligation of American cigarette manufacturers to conduct or support their own careful scientific inquiries into smoking and cancer.

9.4. During the late 1930s-- and unquestionably by no later than 1942-- the scientific evidence that cigarette smoking caused cancer, though not definitive, was sufficient that a reasonably prudent manufacturer of cigarettes should have been warning customers of the potentially harmful effects of its products.

9.5. During the late 1930s-- and unquestionably by no later than 1942-- the scientific evidence on other potentially harmful effects of cigarette smoking, though not definitive, reinforced the obligation of a reasonably prudent manufacturer to warn.

9.6. The published scientific literature offers little if any evidence that American cigarette manufacturers conducted or sponsored research into the potential cancer-causing effects of their products prior to 1953.

9.7. The highly restricted scope of manufacturer-sponsored research on smoking and health during the 1930s and 1940s-- especially the concentration on question of local throat irritation-- is consistent with a concerted strategy neither to test, to corroborate nor otherwise to broach the possibility that cigarette smoking caused cancer." [SOA]

The general plan is to review the literature to determine the justification of the above summary statements. Each one is discussed at the conclusion of this literature review, under Topic F.

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Representative scientific articles selected by Harris, 1923 to 1939. At the outset, it is necessary to recall key references offered by Harris in support of his statements during his Deposition (Exhibit P4900). The following references are listed according to their year of publication, with exhibit numbers. I have added the nationality of authors, general subject, and a four-digit bibliography number ranging from 2500 to 3900 (1925 to 1939 articles). The subject matter includes lung cancer and other health effects such as oral cancer, nicotine and other tobacco constituents. The articles marked "other" have no bibliography numbers and are discussed as a group under Chapter IV (the 1940's).

Key scientific references in Harris' Deposition

AUTHOR/YEAR	EXHIBIT NUMBER	NATION-ALITY	SUBJECT	BIBLIOGRAPHY
Kennaway (1925)	P129	GBR	cancer	2517
Perret (1927)	P189	USA	cancer	2711
Tylecote (1927)	P271	GBR	cancer	2719
Lombard & Doering (1928)	P152	USA	cancer	SGR 2833
Bogen (1929)	P 25	USA	other	2928
Hoffman (1929)	P 25	USA	cancer	2911
Lickint (1929)	P145	GER	cancer	SGR 2927
Mertens (1930)	P164	GER	cancer	3031
Roffo (1930)	P397	ARG	cancer	SGR 3034
Hoffman (1931)	P116	USA	cancer	3131
Roffo (1931)	P224	ARG	cancer	3127
Bogen & Loomis (1932)	P 28	USA	cancer	3227
Cooper (1932)	P 45	GBR	cancer	3230
McNally (1932)	P398	USA	cancer	3224
Roffo (1932)	P226	ARG	cancer	3228
Gross & Nelson (1934)	P 95	USA	other	Chapter IV
Lu-Fu-hua (1934)	P399	GER	cancer	3447
Wright & Moffat (1934)	P382	USA	other	Chapter IV
Schurch & Winterstein (1935)	P245	GER	cancer	SGR 3542
Schurch & Winterstien (1937)	P246	GER	cancer	3734
Schonberg (1935)	P400	GER	cancer	Chapter IV
Sharlit (1935)	P252	USA	other	Chapter IV
Sontag & Wallace (1935)	P260	USA	other	Chapter IV
Thys (1935)	P266	BEL	cancer	3540
Arkin & Wagner (1936)	P 6	USA	cancer	3613
Bogen (1936)	P 26	USA	other	Chapter IV
Blotner (1936)	P369)	USA	other	Chapter IV

Bradford, Harlan & Hanmer (1936)	P 29	USA	other		Chapter IV
Bradford, Harlan & Hanmer (1937)	P 30	USA	other		Chapter IV
Campbell (1936)	P 38	GBR	cancer		3642
Fleckseder (1936)	P 78	GER	cancer		3627
Kennaway & Kennaway (1936)	P131	GBR	cancer	SGR	3632
Bogen (1937)	P 27	USA	other		3754
Kinoshita (1937)	P400a	JAP	cancer		3711
Roffo (1937)	P229	ARG	cancer		3732
Roffo (1937)	P231	ARG	other		3731
McCormick (1938)	P384	CAN	other		3849
Pearl (1938)	P186	USA	other		Chapter IV
Campbell (1939)	P 39	GBR	cancer		3953
Jackson & Jackson (1939)	P385	USA	other		3704
Müller (1939)	P175	GER	cancer	SGR	Chapter IV
Ochsner & Debakey (1939)	P180	USA	cancer	SGR	Chapter IV
Roffo (1938)	P232	ARG	cancer		3847
Roffo (1939)	P237	ARG	cancer		3943
Short, Johnson & Ley (1939)	P255	USA	other		Chapter IV
Total		USA	cancer = 8		
		foreign	cancer = 22		
		SGR	cancer = 7		

The three-letter abbreviations under Nationality mean: ARGentina, BELgium, CANada, GERmany, JAPan, and Great BRitain; SGR Signifies entry in 1964 Surgeon General's Report on Smoking and Health.

American reaction to foreign studies. Harris selected 53 "representative scientific articles" published from 1923 to 1939, and 30 of them were on the subject of tobacco smoking and lung cancer, of which 8 were by American authors, and 22 (73 per cent) were by foreigners. How did such articles, particularly those in German and Japanese, influence American scientific opinion on carcinogenesis? It is my suspicion that because of the impending World War, most American scientists, particularly those who migrated earlier from Europe, were over-critical of German and Japanese scientific publications. Some of the Japanese articles were known to have been fabricated or copied from American laboratories, as can be documented for pharmaceuticals. Prejudices existed because of racial and language differences (see page 23 to 25).

Milestones in epidemiology.

In 1988, the Pan American Health Organization (PAHO) reprinted a collection of over ninety previously published articles appropriately entitled The Challenge of Epidemiology: Issues and Selected Readings. Letters were sent to over a hundred epidemiologists asking them to nominate up to ten works "which they considered landmarks in the development of the discipline, outstanding contributions to the field, or examples of the advancement of an innovative concept". From this vast storehouse of articles and chapters of works, four editors carefully selected most of anthology to develop a well-balanced final version. The four editors also provided discussions "designed to provide a framework for the anthologized works" (8411). A chapter from Major Greenwood's monograph entitled Epidemics and Crowd Diseases was reprinted in the PAHO collection.

Last March (1989), I met Enrique Najera, M.D., one of the editors while vacationing in Spain. The inside cover of the PAHO book stated that:

> "Dr. Enrique Najera is a professor and director of the Department of Preventive and Social Medicine, University of Seville, Spain. He was a consultant for the World Health Organization and the Pan American Health Organization. He has been recently named PAHO/WHO Representative in Brazil.
>
> He studied medicine both at the National University of Litoral in Rosario, Argentina, and at the University of Madrid. Subsequently he studied public health at the London School of Hygiene and Tropical Medicine in England. He is a fellow of the American College of Epidemiology.
>
> He has held several posts in the Ministry of Health and Consumer Affairs of Spain, serving as director-general of Public Health from 1982 to 1985. On several occasions he was Spain's delegate to WHO's and PAHO's Governing Bodies, and he was appointed a member of WHO's Executive Board." [Inside cover, ref. 8802]

Professor Najera comes from a family prominent in the field of Public Health. His father was a Professor of Public Health in Spain who later fled to Argentina to escape Franco's dictatorial Spain. A brother and a sister are

presently with WHO serving in the field of Public Health. It was refreshing for me to listen to an epidemiologist with the following discussion printed in the PAHO collection:

> "Also, nowadays people rely too much on statistics as the only method, forgeting that statistics should be only a helpful tool to ascertain whether events occurred by chance. Yet everyone maintains that things have been scientifically proven if they have been statistically proven. The truth is that you can never prove anything statistically. All you can do is try to eliminate chance, although it can never by completely eliminated - even if it is only one chance in a million. (page 153 of ref. 8802)

The discussion between Drs. Najera and Terris, a co-editor and American epidemiologist, was published in the PAHO book as follows:

"Najera: Using a play as a metaphor is another good way to understand how the concept of the web of causation differs from other approaches of disease causation. For example, in some plays one actor, one main character, practically carries the whole play. This would be analogous to thinking of disease causation in terms of one agent that is more prevalent, more necessary, more important. In other plays, however, there are many actors with equally important roles; you need all of them to preach the play's outcome. This is comparable to approaching disease causation in terms of how people and other factors inter-relate in a complicated web of causation. Some factors would be more important than others, of course, just as in most plays you can have many actors but fewer lead roles. Investigations should aim at understanding all the factors involved. This should facilitate separating confounding factors in the analysis.

Terris: There's another way to look at this: 'The agent is necessary, but not sufficient.'

Najera: When we say 'necessary but not sufficient', however, I think it is important that we analyze necessary for what. In many of the acute diseases, the infectious diseases, we say that the specific agent is 'necessary but not sufficient' because we need the specific agent to name the disease. But in the noninfectious diseases, which agents are necessary? In many cases, we don't really know.

Terris: Yes we do. Cigarette smoking in necessary.

Najera: Not for lung cancer. There is lung cancer without cigarette smoking.

Terris: Very little. Cigarette smoking is almost always involved.
Najera: But the fact is that there is some lung cancer without cigarette smoking. If you have lung cancer without cigarette smoking, then it is not necessary.
Terris: Air pollution, chromates, uranium: there are a number of agents that cause lung cancer.
Najera: Sure, there are a number of agents, but no single one is necessary in the way we are talking about in infectious diseases." (page 151 of ref. 8802)

Professor Najera is familiar with the smoking and health controversy. He related to me the appearance of an article in a journal he just received entitled "Detection bias in the diagnostic pursuit of lung cancer" by Wells and Feinstein (8813). He also mentioned that he is in the midst of examining health records of past employees of Tabacalera (Fabrico de Tobacos at Calle de Fernando built 1728 to 1757, made famous as the setting of the opera Carmen, and presently used as the Administrative Offices of the University of Seville), as well as other workers residing in the same district. Professor Najera implied that his results are contrary to expectations. I did not inquire if WHO or the Spanish tobacco monopoly (Tabacalera) supports his research.

I personally recommend considering Professor Najera as the expert witness to examine the literature, particularly Roffo's publications, that appeared in the 1930's and highlighted in Harris' SOA Report, oral deposition and trial testimony. Since Najera is fluent in English, Portuguese, Spanish and two other European languages, he could readily examine foreign articles and give his opinion. I doubt if any other epidemiologist could match his qualifications and his understanding of the smoking and health literature. The speakers at a recent symposium on Indoor Air Quality (8903) are likewise

potential candidates as expert witnesses if they are knowledgable in Spanish and English.

Harris selection of articles versus the PAHO selection. The milestone articles reprinted in the PAHO monograph did not include any of the more than fifty 1925-1939 articles selected by Harris. The PAHO monograph reprinted four among 293 references in Harris' SOA Report, namely: Bigelow & Lombard, 1933 [SOA 23]; Doll & Hill, 1950 [SOA 52]; Levin, Goldstein & Gerhardt, 1950 [SOA 144]; and Wynder & Graham, 1951 [SOA 289]. On the other hand, PAHO reprinted three articles on smoking and cancer that do not appear in Harris' list and are discussed under the appropriate decade: Doll & Hill, 1964; and Mantel & Haenszel, 1959. Major Greenwood's book entitled Epidemics and Crowd Diseases (3501) was highlighted in the PAHO editorial discussion and is discussed below under Topic A.

Non-applicability of foreign studies.

The PAHO collection contrasted the public heath problems between developed countries of North America, and developing countries of Latin America:

> "Epidemiologists, health planners, and administrators from countries throughout the Americas Region, among others, met at a seminar in Buenos Aires, Argentina in November 1983, to discuss and analyze the role of epidemiology in the developing countries of the Western Hemisphere (8411). After formulating and analyzing ideas and initiatives on the use and future prospects of epidemiology in Latin America, the participants made important recommendations for adjusting epidemiology's practice to current needs.
>
> They agreed that the most important epidemiological issue in the Region has been the change in the health profile of the population as a result of the social, economic, environmental and demographic changes. While communicable diseases persist in most countries of the Americas, they have been increasingly joined by

noninfectious diseases that strike mostly adults and the elderly, by accidents, and by illnesses linked to the workplace and to environmental pollution.

For the industrialized nations, the evolution of patterns of disease spanned more than a century and fell into three fairly distinct stages. The first, marked by infectious diseases associated with poverty, malnutrition, and poor environmental and personal hygiene, gradually gave way thanks to better housing and sanitation, greater availability of safe drinking water, and vaccination services. In the second stage, degenerative diseases such as heart disease, cerebrovascular accidents, and cancer gradually began to replace infectious diseases as the leading causes of death. Finally, the third stage reflects a growing concern with health problems caused by exposure to environmental pollution and to changing social conditions in families, communities, and the workplace which foster violence, alcohol abuse, and drug addiction.

One of the distinguishing features of the health situation in developing countries is that, whereas developed nations went through all three stages in more than a century, developing countries must face all three at once. Consequently, health conditions in the Americas have become a veritable epidemiological mosaic." (page ix of ref. 8802)

The above quotation respected the feelings of developing countries, unlike the summary of Paul D. Stolley in the Bicentenial Issue of the College of Physicians of Philadelphia entitled Unnatural causes: the three leading causes of mortality in America (8803):

"Our knowledge of the epidemiological patterns of disease before written history can only be surmised from rare archeological evidence, but paleopathologists have made educated guesses about the health conditions of our earliest ancestors. These hunger-gatherers have left few signs of their mode of existence, but the paleolithic diet has been reconstructed by knowledge of plants and animals available to them for food. The overwhelming causes of death for paleolithic man were probably infectious diseases and trauma. The short life expectancy and high infant mortality rate resulted in slow population growth, which was further limited by the meager and uncertain food supply. When people became cultivators and established a more secure food supply, the causes of death in all probability remained the same but population growth increased.

With the development of animal husbandry, a new group of diseases emerged as man lived closer to other animals and fell victim to their parasites: tuberculosis, brucellosis, salmonellosis, and perhaps even malaria resulted from the contiguity of

man and domesticated animals. Drought and plant pest caused periodic famine so that population growth was checked in irregular cycles. The revolution in agriculture that came about as a result of the development of tools such as the plow and the invention of the harness produced enough grain to reduce the threat of famine. Increasing population in the cities led to diseases of overcrowding such as the great plague and cholera epidemics. But by the Renaissance and later, the construction of public water supplies and sewage disposal led to a reduction in the incidence of certain water-borne diseases, such as thyphoid and cholera; and a minor increase in life expectancy probably began at that time.

In the Third World countries today, many of the enormous health problems are still similar to those found in the United States at the time of the founding of the College of Physicians two hundred years ago, compounded by urban and rural poverty and unprecedented population growth. Americans, on the other hand, face new health threats that are unique to the developed world.

Today, heart disease, cancer and stroke are the leading causes of death in the United States - and the first two are strongly linked to cigarette smoking as is another leading cause - chronic obstructive pulmonary disease. In fact, we are presently in the sixtieth or so year of an epidemic of smoking-induced disease that began shortly after World War I. Increased cigarette smoking and its related addiction were a direct result both of that war and technological advances in tobacco curing that permitted the mass merchandising of the cigarette pack.

Several million American men were habituated to cigarettes while serving in the armed forces during World War I. This resulted from a policy of pacifying troops that had to endure dreadful conditions in the trenches amid the boredom and horror or war. The inhaling of cigarettes became possible with advances in curing tobacco that made it less harsh, and this, along with a transportation and communication system that allowed marketing throughout the country, resulted in a rapidly developing national addiction.

World War II was longer than the previous war and more people were mobilized. Service in World War II also often led to cigarette addiction. The cost of cigarettes was reduced or subsidized for servicemen, and free cigarettes were sent to soldiers by the manufacturers; indeed, sending cigarettes to "our boys over there" was promoted as an act of patriotism. Following World War II, cigarettes were developed specifically for women (menthol flavored and the like), and the proportion of women who smoked increased.

The result of this national epidemic of cigarette addiction has been a greater loss of life than that due to death from all the wars fought in our entire history. Cigarette-induced disease takes the lives of 350,000 Americans each year; 30 percent of all cancer is caused by cigarettes. Heavy smokers are three-to-four

> times more likely to die of cancer than are nonsmokers and are 15-to-25 times more likely to die of lung cancer. Lung cancer is now the leading killing cancer of women as well as of men - and the epidemic curve is still rising for American women. Cigarettes are also important in causing oral, laryngeal, esophageal, bladder, kidney, and pancreatic malignancies." (pages 196-197 of ref. 8803)

The content of Stolley's article is insulting to developing countries characterized as having the health problems found in the United States in 1788. The quotation is intentionally long because Stolley's ideas about past and present health effects of tobacco smoking are similar to those of Harris' and some physicians during the 1930's. How many physicians in the 1930's wrote like Stolley, or Harris fifty years later?

Authorities on lung cancer.

The above question is answered by searching the literature during the 1930's. Most contemporary medical writers would agree to the two sources of authority on lung cancer:

(a) Monographs and review articles written by experts in the broad area of cancer or lung diseases. Such publications are widely read and quoted in periodicals to serve as background literature. Their authors would have had research experience in the area of cancer or lung diseases and could be practicing internists, surgeons, pathologists, radiologists, or epidemiologists; and

(b) Monographs or review articles limited to lung cancer authored by contributors to original studies on diagnosis, treatment and/or etiology of the disease.

The attention to details by monographers on lung cancer is both helpful and confusing to me because of my desire to reconstruct the evolution of occupational/environmental and hostal factors in etiology of lung cancer. I discovered that German articles not widely known prior to the 1930's became essential to support the concept that smoking was a cause of lung cancer. Harris selected the articles supporting his expert opinion and there are other similar articles he overlooked. I decided to add to the German articles selected by Harris, particularly those that supported the concept that fossil fuel products and combustion emission caused lung cancer. Since I am not very knowledgable in the German language, the description contained in monographs and reviews are quoted.

Almost all scientists who contributed to the literature during the 1930's have passed away. Their publications remain as the only source of documentation of facts and opinions. The most important articles for the decade were new observations supporting causation: (a) the discovery that cancer had a higher incidence in outdoor workers compared to indoor workers; (b) exposure to coal tar and related products in work or home environment resulted in absorption of hazardous substances leading to cancer; and (c) animal experiments support causal relationship between exposure to coal tar substance and development of cancer in the human host. These three groups of observations were available during the 1930's in support of coal tar cancer of skin. However, human studies for lung coal tar cancer were not as extensive as those supporting skin coal tar cancer. Experimental animal studies were available for both skin coal tar cancer as well as lung coal tar cancer.

The suspicion that tobacco smoking caused lung cancer was based on observations that in some patient groups reported from Germany, most cases of lung cancer were male cigarette smokers. Coincidentally, an Argentinian researcher, Ruffo, who had become famous for his work on experimental cancer of the skin, extended his work to skin cancer, by using "tar" derived from tobacco, cholesterol and plant derived beverages. During the 1930's, the total number of publications on tobacco associated cancer was about 30 compared to over a hundred on the subject of coal tar cancer.

The literature during the 1930's can be grouped not only according to the above new observations (a, b, c), but also as to whether a particular scientist agreed or disagreed with earlier investigators. If an earlier investigator (such as Roffo) was mentioned as a statement of fact with no comment by a later author, the citation was meant to inform the reader of background literature. In some instances, authors volunteered their opinions of agreement or disagreement without having conducted an original study or experiment. The literature during the 1930's consisted of monographs, review articles, original reports, editorials, patents, brief commentaries and letters to the editor. As in earlier Chapters, there are abundant quotations rather than paraphrasing its contents.

American Monographers on Lung Cancer.

The most informative sources illustrating the fallacy of Harris' conclusions that relate to tobacco manufacturers are the monographs on the subject of lung cancer and of cancer in general. Harris mentioned only two monographs: Cancer in Massachusetts by Bigelow and Lombard (3301); and

Neoplastic Diseases, A Treatise on Tumors by James Ewing (Professor of Oncology, Cornell University Medical College), Fourth Edition (4001). The former is too limited in scope to qualify as an authoritative monograph on lung cancer, whereas the latter covers all forms of cancer. In an earlier edition (2801), Ewing proposed tuberculosis as the most important etiologic factor. Three editions later, he summarized the literature on etiology as follows:

> "Cancer of the lung is widely distributed over all ages, with a maximum between 40 and 60 years. Many peculiar cases have been observed in young subjects. A congenital multiple tumor was observed by McAldowie in an infant of 5-1/2 months. Other cases have been reported by Hirsch and Ryerson at 6 years; by Nuscheler at 7 years; Simpson at 13 years; and by Horn and by Werner at 18 years. Several cases in children have originated in extensive congenital malformations of the lung (Stoerck).
>
> All authors agree to the great predominance in males, and Stout calculated the ratio as males 83 per cent., females 17 per cent. An influence on heredity, so prominent in experimental studies, has not been traced in human subjects.
>
> To summarize the extensive data on causation: It would appear that cancer of the lung causes between 5 and 10 per cent. of all cancer deaths; that in spite of the absence of statistical proof, the impression of most clinicians should be accepted that the disease has increased markedly in the past two decades, from 1920 to 1940; and that abundant cause for this increase may probably be found in the increased exposure to many forms of irritating inhalations, among which tobacco, coal-tar products, and dusts of many kinds figure most prominently. A suspicion that some unsuspected chemical cancerigenic agents may be involved may be entertained, and this fact together with the large incidence of the disease seems to call for special investigations by private and public agencies into the responsible factors. (pages 874-875 of ref. 4001)

Although some of the names cited above were Americans, most statements were based on foreign studies. For example, the 5 to 10 percent lung cancer of all cancer deaths concealed the fact that European figures were 10 percent or more, whereas American rates were less than 10 percent. Additional quotations from Ewing's monograph appear below (Topics C, D and E) to illustrate that Ewing

relied more on foreign studies in formulating his opinion on etiology of lung cancer.

The above quotation from Ewing's monograph was his own opinion of the important aspects of the literature on the etiology of lung cancer. He formulated his selection, not on the basis of his own original studies as a pathologist on the subject of lung cancer. Ewing did not conduct any of his own original research on lung cancer. Instead, he wrote reviews on trauma as a cause of cancer (3511). A bone sarcoma is named after him.

The following authors are properly referred to as lung cancer monographers because they have written books on the most important aspects of lung cancer, including etiology.

(a) Adler I: Primary malignant growths of the lungs and bronchi (1201). This was the first monograph by an American author (from New York Polyclinic) devoted exclusively to the subject of lung cancer. Unlike Ewing, Adler published his original studies on the clinical aspects of lung cancer. I discovered that one portion of Adler's monograph was overlooked in Chapter I of this review (page 32). Adler proposed an explanation as to why there were more males with lung cancer than females (ratio of 3:1) which was as follows: that cigarette smoking was more prevalent in males than in females, although there was hardly any information on smoking habits of more than 370 lung cancer patients Adler extracted from the literature. Some of these articles are reviewed in Chapter I (pages 34-35) and two more are added to the list: a 1883 case report by Jacobi from New York City (0959) and a 1903 study by Musser from Philadelphia (0958). These two additional case reports, as well as a 1901 case report by Adler (0941) had no information on smoking habits although it was

customary at that time to obtain medical history on personal habits of smoking and drinking (see page 50 and ref. 3001).

Adler conducted rabbit experiments to "offer a contribution to the toxicology of tobacco or nicotine for the purpose of investigating the etiology and very early stages of those interstitial and vascular lesions commonly grouped together under the name of arteriosclerosis" (0956, 0957). Tobacco extract and nicotine was administered orally or intravenously. The experiments were not relevant to smoking and lung cancer.

(b) Evarts Ambrose Graham, Jacob Jesse Singer and Harry C. Ballon: Surgical Diseases of the Chest, including Chapter 27 entitled "Tumors of the Lung", pages 806-852 (3502). The senior author of this monograph, EA Graham (Professor of Surgery, Washington University School of Medicine in St. Louis), subsequently co-authored a 1951 publication with Wynder on the subject of experimental skin cancer induced by tobacco condensate. It is important to note that the monograph by Graham et al did not use any of Harris' 50 representative selection with one exception, i.e., Hoffman, 1929 (P115). Although Roffo had already published his articles on skin cancer in animals as a result of "tobacco tar", the section on "Experimental Carcinoma of the Lung" in Graham's monograph did not allude to Roffo. Instead there was a discussion of positive results of coal tar. The section on "Occupation and Carcinoma" included external mechanical trauma, tuberculosis, pneumoconiosis, and infections, with no mention of tobacco smoking as predisposing factors. In other words, up until 1935, Graham et al ignored publications on smoking and cancer by German, British and Latin American scientists.

(c) Edwin J. Simons: Primary Carcinoma of the Lung (3702). Simons, a clinician from Minnesota, published three articles on lung cancer in the 1930's. He reviewed the literature in a 1937 monograph, and sections on etiology are quoted under Topics B, C, D and E. His conclusions in the chapter on "Etiology" were as follows:

> "Opinion seems to agree that no single agent is the sole cause of pulmonary cancer. But without exception all the 14 etiologic factors so far suggested have one common quality, the production of chronic pulmonary irritation. Chronic irritation, whether simple or complex, may be (1) chemical, (2) mechanical, (3) bacterial, (4) radioactive or (5) as has not been investigated but as occurs in several modern industries, thermal. Several of the causes or possible causes that have been discussed may be classified under two or more of these headings, but all of them fall under at least one.
>
> Even heredity, whether it consists of an anlage or a local or general potentiality to produce malignant new growths, requires, in the opinion of some investigators, chronic stimulation for the activation of malignant proliferation, and this stimulus may be in the form of any of the classified irritants.
>
> Trauma may be classed only as a mechanical irritant, for the mechanical derangement of structures or cells brings chronic irritation into the foreground through the prolonged attempt of the histologic structures to adjust themselves to an alteration in their environment.
>
> The cause of the Schneeberg mine cancers may be subsumed under any of the first four headings given: chemical, since the ores and dust contain cobalt, arsenic, bismuth and iron; mechanical, since the dust contains sharp particles of stone, quartz and iron; bacterial, because of the presence of fungi; radioactive, because the ores are known to have this property.
>
> Influenza, tuberculosis and other chronic lung diseases are properly considered among bacterial irritants.
>
> Tar fractions from roads, tobacco smoke, war gases and motor exhaust fumes are all chemical irritants.
>
> Street dust inhalation, occupational hazards and general sanitary and hygienic conditions may be referred to any of the first three classifications, according as the air inhaled contains mechanical, chemical or bacterial irritants.
>
> In any event, all known etiologic agents have in common the one characteristic of producing pulmonary irritation and, since they are so diverse, the only conclusion possible is that such irritation is the real activating or causative factor in the disease. This is not to say, of course, that all chronic pulmonary irritations issue in carcinomas; and it is to be hoped that

> future research will make this definition of the cause either more specific or more inclusive or both. Meanwhile, it is believed that the reduction of all the presently known facts to one formula is a positive result of the work so far performed." (pages 92-93 of ref. 3702)

Among the more than 500 references, over half are in foreign languages. Among the representative articles selected by Harris, the following are referenced in Simon's monograph: Arkin & Wagner, 1936; Hoffman, 1929; and Kennaway & Kennaway, 1936. The 7 German articles cited by Harris were not in Simon's bibliography although a 1935 publication by Lickint was mentioned instead of the one dated 1929. Simons did not mention any of the seven articles by Roffo although there were over 200 articles in German, French and Spanish in Simon's bibliography. Simons included publications by Hueper and Adler, who were recognized authorities on the subject of lung cancer in the 1930's.

(d) Allan J. Hruby and Henry C. Sweany: Primary Carcinoma of the Lung. This was not a monograph but a comprehensive 44-paged review article with 71 references (3302). Hruby also wrote a chapter on "Primary carcinoma of the lung" in the Practitioner's Library of Medicine and Surgery, edited by George Blaumer, a Yale University Professor of Medicine (3801). Hruby stated in his chapter that McNally's theory (SOA P398, ref. 3224) of increases in lung cancer paralleled the increase in use of cigarettes, and that the causative relation "must be put to a strict test because there are so many users of cigarettes who do not get lung cancer" (p 378, ref. 3801). Hruby and Sweany were from the Research Laboratories of Chicago Municipal Tuberculosis Sanitorium and had the following opinion on lung cancer: "Among the only thing definite is that the cause seems to be similar to that of cancer elsewhere." Tobacco was not

mentioned as a suspected factor; the importance of occupation was instead emphasized:

> "Most cancers are known to be related to some form of irritation, yet there are a large number that cannot be accounted for on this basis. 'Inherent predisposition' seems to play a role, but nothing definite is known so far as human cancer is concerned.
>
> There may be a subtle depletion of some necessary elements in food or other factors that may be gradually undermining normal development. Wells brought up such a question when he said, 'Perhaps there are changes in the incidence of cancer independent of the increased age level of the population.' Otherwise there is no evidence of increase except that caused by the increased life expectancy and possibly by irritation from radioactive dust (Schneeberg and Joachimstal miners) or by influenza, which plays an uncertain role at present.
>
> As to the occupation, there seem to be few instances in which there is any relation to cancer of the lung. Claims have been made that automobile gas, smoke, irritation dusts and tar on roads are contributing causes, but in an analysis of a large number of case histories we were unable to find a tendency in favor of any occupation, trade, profession or station of life. Laborers, office workers and housewives are most affected, but they are likewise the most numerous. Mechanics, automobile workers, painters, stokers and carpenters are involved about in proportion to their numbers. Perhaps the only instances in which the occupation may be suspected are the cases occurring in certain European mines. Incidence of cancer of the lung was shown by Arnstein to be high in workers in the Schneeberg mines, but not in the surrounding population. Schmorl and others studied the problem and reported that arsenic is present in high proportions in the dust of these mines. The dust in also said to be radioactive. Pirchan and Sikl showed this in a study of the pitchblende mines of Joachimstal, Bohemia, across the mountains from Schneeberg. These are medical curiosities, however, and produced no great public health problem. Other minerals, such as nickel, cobalt and bismuth have also been accused, but they do not seem to cause any effect when mined elsewhere in the world." (page 507 of ref. 3302)

Since tobacco was not a recognized etiologic factor, this review by Hruby and Sweany was not used by Harris as a representative citation. On the other hand, the review was referenced by Ewing, monographers (a) Adler, and (l) Hueper.

(e) Lloyd F. Craver: Carcinoma of the Lung. In a 16-paged chapter in "Diseases of the Respiratory Tract, the Eighth Annual Graduate Fortnight of

the New York Academy of Medicine" (3603), Craver reviewed 73 lung cancer patients seen at the New York Memorial Hospital. The sex distribution was 89 percent of cases in men, "a striking preponderance, no doubt to be accounted for by the greater liability of the male to bronchopulmonary irritation by infection, occupation, and use of tobacco." Craver explained male predominance not only because of tobacco, as Adler did, but because of the higher incidence of infection and occupational exposure in males. The paragraphs on this subject are as follows:

> "Assuming that the increase in reported cases is at least partly representative of an absolute increase, and not referable entirely to various factors such as (1) an increasing number of persons surviving to the cancer ages, (2) improved methods of diagnosis, (3) heightened interest in the disease, various writers have sought to explain it on the basis of multiplied hazards to the lung introduced by modern civilization, such as irritation by coal tar products as from tarred roads, automobile exhaust fumes, and the smoke of industrial centers (Dissman). Campbell (3453) exposed mice to inhalation of dust from tarred roads and obtained a marked (tenfold) increase in incidence of pulmonary adenomas.
>
> An examination of the occupations given by our patients shows the following. Twenty-three per cent were engaged in occupations probably entailing irritation of the lungs. One had worked for an oil company as a pipe-fitter, exposed to gas fumes, for eighteen years, having frequently to wear a gas mask during his work. Upholstering, polishing and varnishing of furniture, painting, working with leather in making and repairing of shoes, brickmaking, plastering, working with cement, working with feathers, are among the occupations which this group of patients reported, and which may probably be regarded as causative of bronchopulmonary irritation. Unfortunately in general we lack details as to duration of these occupations, and specific information as to just how much lung irritation they caused in the individual cases. One naturally seeks for some explanation of cancer of the lung in previous respiratory diseases. Here our figures show only 14 cases, or 19 percent in which there was given any history of previous respiratory disease, and only 7 cases in which there was a history of frequent attacks of colds or bronchitis over a considerable period of years, 1 case with a history of 4 attacks of pneumonia and several attacks of influenza, and 1 case with a presumptive history of retained foreign body for twenty-two years. This makes a total of only 9 cases or 12 per cent in which there appeared to have been a severe or repeated long-standing respiratory irritation due to

> infection. We feel that our past histories may not be entirely satisfactory in this respect. The low incidence of influenza is rather striking since considerable attention has been called to the possibility that the influenza pandemic, by its damage to respiratory epithelium in millions of individuals, may have created in their lungs a precancerous state. Winternitz (2001), particularly, noting certain precancerous appearances in the lungs, the result of influenza, ventured in 1920 to query whether there might not be in later years an increase in cancer of the lung.
>
> Claims have been made, both for and against the etiological role of tobacco smoking in cancer of the lung. In 48 male patients with cancer of the lung who gave a statement about their use of tobacco, 31 to 64 per cent were classed as having smoked to excess. In 10 instances this history of heavy smoking was associated with the factor of an occupation that was probably irritating, in 3 instances with a history of repeated or severe respiratory infections, and in 4 instances with both an occupational factor and a history of respiratory infections. On the whole, these figures do not seem very impressive, and seem almost to call for the assumption of some additional factor of special susceptibility of the bronchi to forms of irritation that are probably present to an almost equal degree in subjects who do not develop cancer of the lung." (pages 350-352 of ref. 3603)

The preceding paragraph represented the consensus opinion of those who suspected smoking contributed to several irritating factors. As noted earlier, several monographers did not even mention tobacco as a contributory cause such as (b) Graham and (d) Hruby & Sweany.

(f) Lewis Fox Frisell and Leila Charlton Knox: "Primary Carcinoma of the Lung". The authors, from St. Luke's Hospital of New York City, wrote this 70-paged review article with a bibliography of over 70 references (3705). Although the review enumerated important articles on lung cancer in miners, as well as coal tar painting causing lung cancer in mice, the authors did not regard occupation to play a significant part in their group of 46 lung cancer case reports. Their opinion is discussed under Topic D.

(g) Max O Klotz: Primary Carcinoma of the Lung, an 18-paged review article with 99 references (3802). More than half of citations were devoted

to etiologic factors such as climate, race, occupation, chronic irritation, infections and heredity. The review of chemical and physical agents included over 30 articles on the subject of fossil fuel products and combustion emission:

> "Chemical and Physical Agents. The alleged increase in the incidence of lung tumors has resulted in an analysis of the habits of modern civilization in the hope of discovering some predisposing factors. Thus, smoking of tobacco, exposure to dust from tarred roads and the inhalation of fumes from gasoline engines have all been incriminated. McNally (3224) suggested that nicotine, phenol bodies, pyridine bases and ammonia, contained in cigarette smoke, were irritants which could account for 'cigarette cough,' chronic bronchitis, leukoplakia and the recorded increase in cancer of the lung. Hoffman on the basis of elaborate and confusing statistics, concluded that smoking habits unquestionably increase the liability to cancer of the mouth, esophagus, larynx and the lungs. Hoffman adds the astounding statement that non-smokers are subjected to the same dangers owing to air pollution by smokers. However, it is more than likely that smoking is of absolutely no importance. The available statistics are open to far too many objections to bear any weight. Bronchial cancer is common among non-smokers, and indeed Brockbank (3222) found but 14.5% of his cases heavy smokers, while 21% were non-smokers. Furthermore, if smoking were a factor of any importance it is probable that a striking change in sex incidence would have been observed owing to the rapidly growing prevalence of the habit among modern women.
>
> The development of tarred roads led to much speculation as to a possible etiologic relationship. Some weight is lent to this idea by such observations as those of Kennaway and Kennaway (3632), who noted an increased incidence of cancer of the lung among open air workers exposed to road dusts. It seems remarkable, however, that this observation did not apply to motor vehicle operators who surely suffer a similar exposure. Though a high incidence of lung tumors has been reported from regions where road tarring is not practised, Campbell does not consider this an argument against an etiologic relationship stating that dust from such roads may be carried tremendous distances by the air currents. This cannot, however, be considered tenable in view of reports from communities where the injurious agents would have to be carried hundreds or even thousands of miles. Campbell (3642) found a high incidence of warts which underwent malignant changes in laboratory animals exposed to dusts from tarred roads, but no pulmonary neoplasms developed. Passey and Holmes (3537), carefully analyzing the problem, point out that the alleged increase in lung cancer in Great Britain appeared prior to the tarring of roads. They further

suggest that if the time factor required to produce growths in animals, as demonstrated by Campbell, were applied to man, the effect of road tarring should just now be making itself felt.

Fumes from gasoline engines and pollution of the air in industrial centers can be considered under the same category of etiologic agents as dust from tarred roads. There is certainly no direct evidence to connect lung cancers with the first of these. Though a high incidence of carcinoma of the lung has been noted in some industrial centers where air pollution was great, an equally high incidence has been observed in rural communities. It has also been noted that there is no undue occurrence of the disease among mechanics and garage workers who are constantly exposed to a polluted atmosphere. Although Kimura (2321), reported an adenoma of the lung in a rabbit and an adenocarcinoma of the lung in a guinea-pig following the insufflation of coal tar, Smith, in 1928, was unable to produce pulmonary tumors in mice by exposing the animals to pitch fumes, products of an internal combustion engine, or by painting the skin with gasoline (2826). Although Smith thus found nothing to support the theory that fumes from coal tar or gasoline were of importance in human cases of bronchial cancer, reports such as that of Kawahata are most suggestive. This investigator observed 12 cases of the disease among employees tending furnaces for gas production, where the air contained several tar derivatives with unknown carcinogenic properties. Recently, Seelig and Benignus found 8 adenocarcinoma of the lung in 100 mice exposed to coal soot, while only 1 tumor developed in their controls. It must be concluded, however, that the evidence incriminating inhaled tar products as a cause of cancer of the lung in human beings is as yet far from convincing.

The peculiarly high incidence of bronchial cancers seen among the miners at Schneeberg and Joachimstal, and previously referred to, has also led to speculation regarding the possible presence of a specific agent in the mine dusts. The dusts of both mines are radioactive and, in addition, contain bismuth, cobalt, nickel and arsenic. Analysis of lungs obtained at autopsy from miners at both these sources have proved entirely negative as to radioactivity and any significant chemical content. As pointed out by Pirchan, these negative results do not rule out the possibility of a chemical factor, no trace remaining owing to its rapid removal. Arsenic has been suspected because of its known carcinogenic effects upon skin. Schmorl was impressed by the constant and marked pneumoconiosis found in association with the growths at Schneeberg and he originally believed that physical irritation was the probable cause of the tumors. Later, he suggested that the radioactivity as well as the arsenic content of the dust might be additional factors. Mice exposed to the mine dusts showed only negative results. The Schneeberg mines are described as damp, infested with a variety of

> moulds and conducive to the development of chronic bronchial catarrh which in itself might be of some importance. At Joachimstal, pneumoconiosis was not a prominent feature, as shown by Pirchan, but the lungs of miners dying with pulmonary growths presented a picture otherwise morphologically identical with that described by Schmorl. Pirchan was inclined to consider the radioactivity of the mine dusts and air as the most probable specific agent. It is said that the incidence of carcinoma of the lung is decreasing at Schneeberg following the introduction of respirators, which suggests that the factors reponsible for the pneumoconiosis are also related to the production of the growths. On the other hand, respirators have been used at Joachimstal and the incidence of tumors remains high, while pneumoconiosis is uncommon. This problem, though fascinating, is confusing in the extreme and can by no means be considered settled." (pages 450-451 of ref 3802)

Klotz, a pathologist from the University of Toronto, conducted research on association of silicosis and carcinoma. Other publications reflected his own favored theories (see Topic E).

(*h*) R. J. Behan: Relation of Trauma to New Growths (3901). Dr. Behan, a surgeon from Pittsburgh, Pennsylvania, obtained his medical degree from the University of Berlin. He stated that the emphasis of his book was on medico-legal aspects. Since he was a Governor of the American College of Surgeons, it is possible to verify whether Behan migrated as a physician before World War II to flee Nazi racist policy, or that he was unable to enter an American medical school because of his race. At most medical schools in the East Coast during the 1930's, there were racial prejudices in acceptance of medical students and appointments of professors. In any event, the pertinent portions of the book has been copied. It should be noted that the book was deemed "of value to judges, lawyers, referees of compensation courts, adjustors, and representatives of insurance companies, who, as a class, try to fulfill their duty and are zealous in the protection of the rights of their

clients and suppliants. This personal urge, in most instances does not overcome their sense of fairness" (Preface). Trauma refers not only to physical, but also chemical agents. The chapters on the respiratory system and occupational cancer did not mention tobacco.

(i) Frederick L. Hoffman: Cancer and Diet (3701). This book was not selected by Harris in his list of representative articles. Instead, two articles by Hoffman (1929 and 1931) were cited by Harris. The publications of Hoffman are discussed under Topics C and E.

(j) Charles P. Emerson: New Growths in the Lungs, in Cecil's "Texbook of Medicine", second and third editions (3002, 3401). The earlier edition contained a statement on the rarity of primary tumors compared to the more common metastatic tumors. Four years later, Emerson, a Professor of Medicine at the University of Indiana, changed his opinion of rarity.

> "Cancer of the lung explains from 5 to 10 percent of all cancer deaths and is the commonest form of intrathoracic tumor. Males are affected five times as often as females.
>
> The majority of lung cancers are primary in the bronchial epithelium, bronchial mucous glands, and alveolar epithelium. Their metastases often reach the mediastinum, central nervous system and abdomen.
>
> Among the most interesting of lung cancers are the very acutely developing ones seen among the cobalt miners of the Schneeberg Region of Saxony, which now are attributed to pneumonoconiosis from radioactive stone dust. In the lung are found also metastases from cancers primary in other organs.
>
> Our ideas of primary malignant disease of the lungs have in too large measure been gained from a retrospective study of cases and, therefore, the details of the early clinical course of the disease are in large measure lacking. As a rule, the possibility of cancer is seldom considered until all other possibilities have been excluded, and the tumor has usually progressed so far that various secondary conditions, such as bronchiectasis with its subsequent supprative and possibly gangrenous processes, are dominant." (page 905 of ref. 3401)

The argument on the primary cause of Schneeberg lung cancer continued as to whether the culprit was radioactivity, or silica, or both. Two decades later, after completion of animal experiments, the primary causative factor was settled as radon.

(k) B. M. Fried: Primary Carcinoma of the Lung (3201). This book was preceded by a 130-paged review article (3101) and followed by revisions during the next two decades (4801, 5801). Fried wrote over a dozen articles on research on lung cancer patients, such as those admitted to Peter Bent Brigham Hospital (3033) and Montefiore Hospital (3441). He was the only monographer who had written from the 1930's to 1950's emphasizing changes in concepts of pulmonary carcinogenesis. In the first edition of Fried's monograph, he summarized the chapter on etiology as follows:

> "The study of the etiology of cancer comprises three distinct phases: (1) The extrinsic factor, that is the tissue "injurer" which is brought from without (and possibly also from within); (2) the intrinsic factor, that is the 'readiness' of the host to undergo cancerisation; and (3) the intimate mechanism of the transformation of the cell from a physiologic into a pathologic malignant status.
>
> Whereas the last two points are not yet understood, the first is thought to be fairly well established. Today 'irritation' (the theory expressed for the first time by Virchow) is regarded as an essential factor in the causation of an epithelial malignant condition. Chemical, thermal, and physical substances of different kinds and likewise parasites and bacteria are considered as agents playing predisposing roles in the development of a neoplastic disease.
>
> It is remarkable, however, that the 'irritation' does not lead abruptly to the development of a malignant disease. Experimental and clinical observations have shown that there occurs a rather considerable 'pause' or latent period between the time the injury was applied and the appearance of the disease itself. Largely because of this fact the factors or agents which have virtually determined the disease cannot be ascertained. This holds true particularly in the so-called 'inaccessible' (internal) cancers.
>
> An analysis of the life histories of the 47 patients with bronchiogenic cancers studied by the author failed to point toward any one of the factors referred to as being the probable agent

> causing the malignant disease. In some instances, the patients had suffered broncho-pulmonary disturbances for a few years prior to the present illness. This has been often interpreted as the preceding 'chronic irritation' which has led ultimately to a malignant condition. It is very likely, however, that in many patients these symptoms were really due to the already existing pulmonary cancer. Bronchiogenic cancer usually runs a protracted course, and marked subjective symptoms often appear only when the tumor has attained large dimensions or has been secondarily altered, that is, has undergone degeneration. The tumor, then, in its slow and silent advance usually buries with it the particular agent which might have inaugurated its growth, but it is beyond doubt that irritation is as necessary a predisposing factor in the causation of cancer of the lungs as it is in cancer of other organs.
>
> Apparently bronchiogenic cancer is merely a part of the entire problem of malignant dsease, and its true etiology will not be known until the final solution of the whole problem is at hand". (page 23-24 of ref. 3201).

Harris representative references did not include any from Fried's 1932 nor 1948 Edition. In both editions, there were references that suspected carcinogenic action of tobacco use, described by Germans prior to 1930. The pertinent quotations from Fried's monographs are quoted below under Topics C and D. Like other monographers on lung cancer, Fried alluded to Hueper's publications on lung cancer.

(1) Wilhelm C. Hueper: Experimental and Environmental Cancers of the Respiratory System (6601). This was the title of a 1966 monograph that reviews German articles prior to and during the 1930's. Hueper, after his earlier publications on lung cancer (2623, 2933), wrote several articles during the 1930's on the following topics: leukemia, growth factor, experimental breast tumor, experimental urinary bladder tumor, experimental thesaurioses, and industrial chemicals causing human cancer. The 14 articles are discussed below under Topics C, D and E, and in Chapter IV.

European Monographers on Lung Cancer.

There were one or two monographs from each of the following countries: France, England, Italy, Germany and Switzerland. It is important to note that all of Harris' representative articles were not used by European monographers except in two instances: British author Davidson cited Hoffman 1929; and French authors Sannie & Truhaut cited Roffo and Lickint. Most European monographers were aware of Adler's and Hueper's publications.

(m) R. Huguenin: Le Cancer Primitiv du Poumon: etude anatomio-clinique, 330 pages (2802)

(n) Herbert Seele: Das Primare Lungencarcinom (Dissertation Facultat der Friedrich Wilhelms - Universitat zu Berlin), 31 pages, 1936 (3601). Since there were German articles in the references that mention tobacco and cigarette smoking, and German authors Lickint and Mertens cited, this monograph needs translation into English. American, British or Latin American authors were not mentioned.

(o) M. Davidson: Cancer of the Lung and Other Intrathoracic Tumors, 173 pages (3003). Selected citations are under Topics C, D, and E.

(p) G. W. Giesewetter: Ueber das primäre Lungencarcinom, 32 pages (3102). A translation is needed.

(q) P. Verga & G. Botteri: Il Carcinoma Primitivo del Pulmone (studio anatomo-istologico e clinico), 224 pages (3103). A brief paragraph devoted to tobacco (page 39) referred to the monograph in French by Huguenim. Roffo was not mentioned, but Kumura was cited in the discussion of coal tar intrabronchially.

(r) C. Sannie & R. Truhaut: "Les agents chimiques cancerigenes." The authors, from Cancer Institute Gustave Roussy, Paris, wrote this 37-paged review with 125 references including Roffo, Lickint and others who worked on tobacco tar (3402).

(s) Ali Soliman: "Contribution a l'etude du Cancer Primitif du Poumon", 31 pages (3703). A translation is needed.

(t) Hilaire Roume: Contribution a l'etude du Cancer primitiv du Poumon, 132 pages (3804). This doctorate thesis submitted to the Faculty of Medicine at Marseille contained 7 case reports and a review of the literature, mostly by French physicians and by a Japanese (Nakano), on the subject of experimental lung cancer. The score of references in English did not include Adler's nor Ewing's monographs. There was a discussion of "Le cancer du Goudron" (coal tar cancer), but no mention of tobacco.

Japanese Monographer on Experimental Cancer.

There is only one available review article by a Japanese pathologist written in English:

(u) Riojan Kinoshita: "Studies on the Carcinogenic Chemical Substances", 62 pages (3711), This review cited several articles in Japanese which need translation to English. The contents of Kinoshita's article and his Japanese colleagues are discussed below under Topics C and D. Meanwhile, it is important to mention once more that after the Japanese invasion of Southeast Asia, physicians in China, Korea, Australia and the United States became highly prejudiced against scientific publications originating from Japan. Some of the

atrocities and prejudices were recalled by veteran groups during the funeral of Emperor Hirohito in February 1989.

Latin American Monographers on Lung Cancer.

From 1938 to 1942, there were three monographs written in Spanish: two from Argentina, and one from Cuba. Although Roffo's (from Argentina) publications were available prior to 1938, he was not mentioned in two Latin American monographs. However, Llambes et al (from Cuba) wrote two pages on tobacco as a cause of lung cancer and cited the following references: Roffo, 1935; Thys, 1935; Schurch and Winterstein, 1935; and Lu-Fu-Hua, 1934. Palaccio and Mazzei cited Hueper (1929) but did not mention the contents challenging tobacco as cause of lung cancer. There was a brief discussion of fossil fuel products and combustion emission but Llambes et al did not express their opinion as to whether their own 102 cases supported the importance of acute irritants, pre-existing diseases or familial predisposition to cancer. There were 15 case histories detailed in the monograph, of which 10 were tobacco smokers, as well as alcohol drinkers. Portions of these three monographs, as well as a score of articles in Spanish and Portuguese, need to be reviewed by a trilingual scientist, such as Enrique Najera (see above) who can also review the 45 articles by Roffo on the subject of experimental cancer discussed under Topics C and D.

(v) Jose de Filippi: El Cancer del Pulmon, 293 pages (3803).

(w) Julio Palacio and Egidio S. Mazzei: Tumores Primitivos Malignos Bronco-Pulmonares, 401 pages (4002); see pages 21-26 and case histories on pages 200-298.

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(x) Juan J. Llambes, Pedro L. Farinas, Luis Farinas and Vicente Banet: Carcinoma Primitivo del Pulmon, 507 pages (4203).

Summary of lung cancer monographs. All 24 monographs listed above were not mentioned in Harris' SOA report. He could not have missed them because all were listed in Index Catalogue of Library of the Surgeon General's Office (see page 11). Three-quarters of the monographs do not mention tobacco smoke as a suspected cause of lung cancer, including the two written by Argentinian physicians, who were undoubtedly aware of Roffo's publications on tobacco tar. There were only three monographs that mentione Roffo: 1934 review by Sannie and Truhaut; 1942 morograph by Cubaan scientists Llambes et al; and the 1940 monograph by Ewing. The latter mentioned Roffo in the text but not in the bibliography, signifying that Ewing made a last-minute alteration to his monograph. With the exception of the three above, the group of over thirty key scientific articles from 1923 to 1939 selected by Harris were not mentioned in the 24 monographs, suggesting that causative role of tobacco smoking was ignored by almost all monographers.

A. INCREASING INCIDENCE OF CANCER

During the 1930's, some epidemiologists continued to report the increasing incidence of cancer deaths which was attributed to several factors, including industrialization, use of tobacco, alcohol and other beverages, imbalanced diet, improvement in antemortem diagnosis, increase in percentage of autopsies in hospital deaths, and aging of the population. Major Greenwood published his monograph on epidemiology entitled Epidemics and Crowd Diseases (3501). He emphasized the influence of social classes on cancer incidence which had been ignored by his colleagues. Greenwood was characterized by PAHO editors as follows: "Major Greenwood preceded Bradford Hill at the London School of Hygiene. In 1935, he published a book that not only contain chapters on tuberculosis and other contagious diseases of great concern, but also chapters on cancer and psychological causes of illness. Greenwood made it clear that epidemiological concepts were transferable from one kind of disease to another." (page 87 of ref. 8802)

In the chapter on influence of occupation on morbidity, Greenwood had the following comments:

> "It is partly because of the leveling down of mortality in the human population that the present tendency of research is to concentrate upon morbidity rather than mortality. The desirability of this, its essential importance from the standpoint of preventive medicine, is obvious enough, yet it is well to guard oneself against exaggeration. More than seventy years ago Walter Bagehot in a criticism of Charles Dickens made this comment:
> 'He began by describing really removable evils in a style which would induce all persons, however insensible, to remove them if they could; he has ended by describing the natural evils and inevitable pains of the present state of being, in such a manner as

must tend to excite discontent and repining. The result is aggravated, because Mr. Dickens never ceases to hint that these evils are removable, though he does not say by what means. Nothing is easier than to show the evils of anything. Mr. Dickens has not infrequently spoken, and, what is worse, he has taught a great number of parrot-like imitators to speak, in what really is, if they knew it, a tone of objection to the necessary constitution of human society.'

These parrot-like imitators have multiplied enormously in the last seventy years, and their parrot-like insistence upon research into this or that evil of modern life is sometimes a serious obstacle to real research, because, having no conception of the complexity of the problem of interrelated group factors and a simple faith in the doctrine that what is not recorded did not happen, they are apt to believe that some particular evil "(noise,' for instance) is both easily remediable and quite new." (page 126 of ref. 3501)

The chapter on cancer and social classes was essentially a criticism of applying statistics derived from one country into another, which was a major shortcoming during the 1930's.

"This method of global comparison is open to the theoretical objection that some particular occupation, if it is both very populous and economically homogeneous, might colour the statistical average of the class containing it too strongly, and to the practical objection that it gives no indication of the intra-class range of variation.

Tables 73 and 74 comparing the experiences of England and Wales and the Netherlands (with some other countries) bring this out. Here we have two countries suffering not widely dissimilar tolls of total mortality from malignant disease, yet contrasting greatly in respect of cancer of the female breast and sexual organs. An expert committee of the Health Organization of the League of Nations spent much time and labour in seeking to explain this discrepancy. The investigation verfied the facts; it made it clear that no simple explanation (such as better facilities, or better use of facilities, for radical treatment) was adequate, and it got no further. If we could explain this discrepancy we should, I imagine, be near the center of the cancer maze. That we cannot is a warning to those who would solve the problems of malignant disease from an arm-chair. I suppose to most readers this is an unsatisfactory account. We seem to know a little about a great many things of importance and a great deal about a few things of no special importance, but the epidemiological-statistical method has, so far, reached no clear-cut conclusion which is of general aetiological

> importance. That is, I think, a just criticism, yet I am not pessimistic.
>
> The answer to the young lady's question to Babbage, of calculating machine fame: 'Please, Mr. Babbage, if you ask the wrong question, will it give you the right answer?' is still 'No.' Even in this country approximately accurate statistical data of mortality from cancer are a product of less than a generation. The accuracy is still only approximate.
>
> Here my sketch of crowd-diseases must end. A great many important objects have been brought into the picture, but many have been omitted.
>
> Among crowd-diseases in the grand manner, malaria does not yield in importance to plague; among crowd evils always with us, whooping cough is not less deadly than measles, while traffic accidents (which surely come within my definition of a crowd-disease) are a good deal more deadly. The trouble is that when one enlarges the definition of epidemiology one is theoretically committed to a treatise on all the bad habits of mankind, and so must practise all illogical moderation.
>
> Perhaps, however, enough has been said to enable an interested reader to go further by himself. I hope to have taught him that this is a field of study not only as important but as interesting as others universally agreed to be within the circle of general culture. The subject is one which the non-professional reader has no excuse for neglecting on the ground that it is dry and technical. If and when all educated persons are as familiar with this kind of medical history as they are with political history, the level of discussion of social legislation will be raised and less attention will be paid to the dicta of 'experts', 'well-known Harley Street specialists,' or even 'professors,' to the benefit of all concerned. (pages 124, 375-376 of ref. 3501)

Major Greenwood, in spite of his criticism of applying epidemiologic statistics derived from one country to another, was not fully appreciated during the 1930's and 1940's. For lung cancer, statistics derived from Germany were applied to the United States. The Public Health policy of changing personal habits among the British was not adaptable in Massachusetts and neighboring states.

Cancer Mortality in England

In approaching the question of possibile relationship between work environment and cancer mortality, Turner and Grace conducted statistical analysis of mortality for 12 occupational groups of males in Sheffield from 1926 to 1935. Of these groups, cancer mortality experienced by clerks, business and professional men was significantly exceeded by cancer mortality of the following groups: engineers, machiners, cutlers, steel foundry and furnace workers, grinders and sandblasters, workers in precious and non-ferrous metals, workers in transport and communication, and coal miners (3811).

Occupational influence on lung cancer mortality. Turner and Grace grouped cancer of the larynx, lungs and bronchi and mediastinum together under the heading of "Cancer of the Respiratory System":

> "Three occupational groups show significant excess of cancer of the respiratory system. In the case of transport workers the significance figure is only 1.9, which falls below our statistical standard. It will, however, be seen later that transport workers suffer a significant excess of cancer of the lips and tongue and cancer of the tonsil. It is probable therefore that the excess of laryngeal cancer is real and that the factor causing the excess of cancer in transport workers in these three sites is exposure to wind containing grit and dust. This view is supported by the findings of Young & Russell (1926), who also show that agricultural labourers suffer a very gross excess of cancer of the lip and tongue and a smaller but still significant excess of cancer of the larynx. It should also be remembered that a small proportion of the transport workers in Sheffield actually work in the steelyards, and some of these will previously have been steelworkers.
>
> Furnace and foundry workers suffer the greatest excess of respiratory cancer, and this excess is found in larynx, lung and mediastinum. The adverse factors in their work environment are (1) gases and smoke, (2) heat, (3) dust, in this order.
>
> Turning to the other section of iron workers, namely, the engineers, turners, cutlers, etc., who work the cold metal, it is seen that they also suffer a significant excess of respiratory cancer in larynx, lung and mediastinum. The possible adverse factors in their work processes are (1) iron dust and chippings,

> (2) lubricating oils and solutions, particularly used in turning processes. It is the operation of the latter, together with the trauma of the skin by metal particles, that causes engineers to occupy such a high place in the list of occupations liable to industrial dermatitis (Legge,1934).
>
> Both sections of steel workers suffer a significant excess of mediastinal cancer. The difficulties of differentiation of a primary mediastinal cancer from one secondary to a primary lung focus make it only to be expected that any group of individuals showing an excess of lung cancer will also show an excess of mediastinal cancer. Under the circumstances the excess of mediastinal cancer can be taken to support the fact that intrathoracic cancer is significantly excessive, but could hardly be taken as a real proof of the excess of true primary mediastinal cancer. The occupational hazards of these two sections of steel workers will be further discussed later.
>
> Grinders also suffer a significant excess of respiratory cancer, but this is only statistically significant in cancer of the lungs and bronchi. Their occupational risk is mainly abrasive dust for the most part silica to a much smaller extent there is the inhalation and ingestion of metal dust from the article ground." (pages 94-95 of ref. 3811)

The above discussion was typical of difficulties in proving that certain occupational exposures, instead of personal habits, caused cancer of the respiratory tract. The role of silica and other forms of inorganic dust in carcinogenesis is discussed under Topic E.

Habits, home life, dietary and family histories. In 1928, an appeal was made in the London medical press for voluntary cooperation of physicians, surgeons and specialists in completing a schedule of questions relating to individual patients suffering from cancer, and to patients of the same ages not suffering from cancer to serve as controls. Stocks and Karn reported the results of a series of 462 cancer patients and 435 controls (3330):

> "The two series were proved by statistical tests to be homogeneous as to age, occupational and civil status, general activity and place of residence in respect of urbanisation.
>
> No significant difference was found between the series in regard to the elevation or dampness of the sites of their houses, the keeping of a dog, or the occurrence of previous cases of cancer

in the house in so far as these were known to the patients. Slightly excessive rates of infestation of the houses with rats, mice and cockroaches, and frequency of keeping a cat, were recorded by the cancer patients, but the excess was not statistically significant in any instance and no conclusions can be drawn. No difference was found between cancerous and cancer-free patients of the same sex and age in regard to their temperament or nervous balance prior to illness.

No association was found between the habitual frequency of evacuations prior to illness and the occurrence or non-occurrence of cancer either of the digestive tract or of other organs, but although constipation did not tend to precede cancer in general, when cancer did occur it was slightly more likely to have been preceded by constipation if located in the digestive tract than if located elsewhere. The habitual taking of purgatives prior to illess was not found to have any significant association with the occurrence of cancer.

Men with cancer at ages under 65 were more likely in the aggregate to have been pipe smokers, and therefore less likely to have been heavy cigarette smokers than other men of the same ages, but no significant association was found between pipe smoking and cancer of sites other than the tongue, lips, mouth and pharynx.

Cancer was not positively associated to any significant degree with the previous occurrence of rheumatism, diabetes, haemorrhoids, chronic dyspepsia, gall-stones, jaundice or appendicitis; in women, on the contrary, there was a significant negative association with previous dyspepsia and jaundice.

Each patient having been asked how frequently he or she had been in the habit of partaking of different articles of diet, analysis of the replies revealed no consistent significant differences in frequency between the cancerous and cancer-free patients for any of the following: white or brown bread, fresh beef or mutton, chilled beef or mutton, bacon or ham, liver, pork or sausages, tinned meat, fresh fish, herrings or kippers, tinned fish, potatoes, lettuce, tomatoes, fresh fruit, tinned fruit, butter, cheese, cream, sugar, pepper, bottled sauces, vinegar, tea, coffee, mineral waters, wines, spirits or cider.

The cancer patients had, according to their own statements, been accustomed to drink unboiled milk less frequently on the average than the control patients, and to a significant degree, but this was not the case for boiled milk. A similar negative association was suggested by the statistics for whole meal bread, and for carrots, turnips, cauliflower, cabbage, onions, watercress and beetroot, and though the degree of this association was not large enough to be statistically significant for any one of these vegetables taken alone, its occurrence for all the vegetables in all the groups of patients seemed to be inexplicable from random causes.

> Daily beer drinking was found to have been more frequent to a significant extent amongst the cancer patients, and a considerable correlation was found between it and the location of the cancer in the mouth, pharynx, oesophagus and neighbouring parts. Cancer was much more frequently represented in the group of men who drank beer daily and seldom drank unboiled milk than amongst those who took unboiled milk frequently and beer seldom or never, and the distributions were such as would be expected if the effects of the one neutralised the effects of the other.
>
> The above findings in regard to milk and vegetables, whilst they are in no sense established, suggest that further research, experimental and statistical, should be carried out to confirm or refute them, since if the negative association is a real one and not due to a failure to attain what Professor Edgeworth called 'ideal randomness' in the selection of the two samples of patients compared, important practical effects in the reduction of cancer incidence might conceivably be brought about by a modification of diets, or, better still, some substance preventive of cancer might be isolated.
>
> When the frequency of cancer in the parents, brothers, sisters, uncles or aunts of cancer patients was compared with the frequency in the same relatives of control patients, at the same ages, no significant differences were found. No evidence of hereditary transmission of cancer was given by the records, nor any evidence that a history of cancer in one or both parents, or in several relatives, increases the risk of cancer to any measurable extent." (pages 279-280 of ref. 3330)

The above conclusions refer to all patients with cancer regardless of organ involved. The conclusions on American diet and habits obtained by Hoffman (3131) need to be contrasted with the above conclusions relating to Britishers. The design of a case-controlled study reflected the standards of the decade and failed to define any role of cigarette smoking in causation of cancer. Harris, in his SOA report, criticized the tobacco industry for not conducting epidemiologic studies, ignoring the fact that protocols were not refined enough to obtain statistically significant answers.

Cancer Mortality in the United States

Harris cited two publcations by Lombard and associates in support of his

conclusion that "studies of patient populations confirmed the clinical finding that tobacco use was more common in certain oral cancer patients than in comparison subjects" (SOA 3.9). The subject of oral cancer is discussed under the next decade, Chapter IV. However, publications of Lombard et al related to the general subject of cancer mortality in general, and properly belongs to this section. Although only two were used by Harris (2833, 3301), there were four other articles by Lombard and collaborators that require consideration (2730, 2839, 2951, 3845).

My recent visit to Boston revealed several sources of information on public health aspects in Massachusetts: a history of Massachusetts General Court (8401), Public Health Trials in Massachusetts (8804), Major Health Problems in Massachusetts (8001), Chemical Hazards on the Job, a booklet on worker's rights under the Massachusetts Right-to-Know Law (8701), and the Massachusetts Substance List (8702). It has become apparent to me that Harris' publications and expertise are not appreciated by public health and epidemiologist in Massachusetts. The contents of these publications and their influence on Harris' publications and vice versa are discussed in Part Four.

Cancer studies in Massachusetts. The program of cancer control started in 1927. The Massachusetts Department of Public Health conducted the first state sponsored cancer studies:

> "In 1842 the cancer death rate was 13 per 100,000; in 1860 the rate was 26; in 1900 it was 71; while in 1926 it was 126.8. That this increase is *not* all real is obvious. In the early years many deaths which were undoubtedly due to cancer were certified as senility, stomach trouble, or unknown cause. Even at the present day, there is still confusion in diagnosis, and the rate of 126.8 is probably too low, but when allowance has been made for improvements in diagnosis and better certification, there still remains a definite increase in the cancer death rate. This increase in rate

present in both sexes, is greater among males than females. In the female group there has been a tendency for the curve of cancer death rate to flatten. This was so marked in 1926 that there were 300 less deaths than might have been expected from the study of the long-time trend.

In the years 1920 to 1925, Massachusetts had the highest cancer death rate of any state in the Union, when adjustments had been made for age and sex distributions. In this same period, New York was second, Rhode Island third, and Connecticut fourth, while many of the southern states had very low rates." (page 414 of ref. 2839)

A correlation was shown to exist between the density of population and the adjusted cancer death rate in Massachusetts. It was concluded that like England, cancer was a "crowd disease" (see above under Greenwood). Economic social condition was a factor in the causation of cancer. The foreign-born had much higher death rates than the native-born of native parents in cancers of the buccal cavity and stomach. However, the number of lung cancer cases was not sufficient to determine influence of social classes, nativity and personal habits. The smoking habits of patients with buccal cancer are discussed in Chapter IV.

The history of public health service in the state of Massachusetts was stormy during the 1920's when funding for cancer study was debated in the state legislature. Priorities were debated in favor of non-immigrants which was against the policy of the State Commissioner of Health. It was rumored that "he took his own life" because of the strain of administering a demanding public health program (7201).

Late in the 1930's, it became necessary to verify the accuracy of cancer death records in Massachusetts. MacDonald reported results of personal interviews with families and physicians for a third of the 6,153 cancer deaths. Her conclusions were as follows:

> "The analysis of these data indicates that in Massachusetts identification of cancer deaths is sufficiently accurate to warrant statistical compilations on age, sex, nativity, and the disease as a whole. There is a considerable error in exact location of cancer and a large error in duration of disease, and the statistician should not draw conclusions on these data without making corrections for errors known to exist." (page 824 of ref. 3845)

After ten years of collecting health statistics, the cancer death records for lung cancer could not be accurately analyzed because of uncertainty in location of primary cancer.

Metropolitan Life Insurance study on cancer mortality. Harris used the anonymous report entitled "Cancer of the lung, a growing health problem" (3911), as one of 26 references in his response to ERR question: "Let me turn to part 7 of your report about diseases other than lung cancer. Are there any of these diseases for the period covered by your report there was more evidence of an association of cigarette smoking than in the case of lung cancer?" (p 49, ERR). The article that appeared in Statistical Bulletin did not relate to "diseases other than lung cancer." Harris may not have been aware that this article on lung cancer questioned the role of tobacco smoking as a contributory factor to the increase in mortality of lung cancer during the 1920's and 1930's. Among the industrial policyholders of the Metropolitan Life Insurance Company, the standardized death rate for lung cancer at ages 45 to 74 rose from 2.6 per 100,000 in 1917-1918 to 15.0 per 100,000 in 1937-1938.

> "A striking feature of the trend for lung cancer is the much more rapid rise of the death rate for males than for females, as illustrated in the accompanying chart. In fact, among white males the mortality recorded for malignant tumors of this organ increased at a faster pace than that for any other site. As a result, whereas 20 years ago the death rate from cancer of the lung and pleura among white males was less than 1-1/2 times that for white females, the current ratio is 3 to 1. This is a remarkable situation, for which no ready explanation suggests itself.

How are these facts to be interpreted? If the upward sweep of the mortality curve actually represented a corresponding increase in the incidence of the disease, the situation would indeed be alarming. But such is not the case; it is highly probable that a large part of the increase, if not all, is due to the more frequent recognition and reporting of this cause of death. In the past 20 years a growing number of physicians have become more alert to suspect the disease and have become better qualified to diagnose it. In addition, the development and increasing use of diagnostic aids, such as the bronchoscope and the X-ray, have further facilitated the discovery of cases of lung cancer. Difficulty in diagnosis tends to arise from the fact that this disease may simulate other diseases of the lung, and because of advances in diagnostic skill and technique, an increasing number of deaths, which in earlier years would have been incorrectly diagnosed and reported as due to tuberculosis, pulmonary abscess, or pneumonia, are now recognized as due to cancer of the lung and are so recorded. Another factor to be considered is the more frequent practice among physicians to attribute deaths from lung cancer to the organ of primary involvement, instead of the site of metastasis. In view of the frequent tendency of lung cancer to metastasize, this factor may be of some importance. All of these developments have contributed to a spurious increase in the mortality from cancer of the lung and pleura.

The question then arises, is any of the increase in the mortality of this disease real? There is a sharp division of opinion among authorities on this question, and no categorical answer is possible. A number of those who believe that the disease is actually becoming more prevalent, have attempted to correlate the alleged increase with such factors as exposure to dust from tarred roads, the inhalation of polluted air, and the smoking of tobacco. The evidence offered in support of such views falls far short of being convincing. As regards smoking, for example, it is a matter of common knowledge that the habit since 1917 has become relatively more prevalent among women than among men. If smoking were of appreciable etiological significance, we might expect the death rate for the disease to increase more rapidly among women than among men. As already indicated, the reverse has actually been the case. At present it appears doubtful that smoking is a factor of etiological importance in cancer of the lung." (pages 7-9 of ref. 3911)

The anonymous article was probably based on the monograph "The Mortality from Cancer, a study of mortality experience among the industrial policyholders of the Metropolitan Life Insurance Company, 1911 to 1935," by Dublin and Lotka

(3805). The role of cigarette smoking was not mentioned in the book (pages 165-225, 553-561) nor in other articles by Dublin and his collaborators (2531, 2841, 3912). The remainder of the book, as well as other articles by Dublin, need to be examined to obtain the authorship of anonymous articles. This article cited wrongly by Harris, can be useful in discrediting his SOA statement that by 1939, tobacco companies should have conducted research on smoking and lung cancer. The discussion of whether there was a real increase in lung cancer incidence in the United States is continued under the next Topic.

Cancer mortality rates in various states. The U.S. Census Bureau initiated annual causes of death summaries in the late 1910's. By the 1930's, the certification of cancer in general, and of lung cancer in particular, continued to be questioned for accuracy. The debate whether the percentage of lung cancer relative to all cancer deaths continued through the next two decades, until antemortem diagnosis became accurate enough to demonstrate comparative mortality rates among states.

B. CASE REPORTS OF LUNG CANCER

During the 1930's, there was a considerable increase in number of lung cancer articles, more than twice the number published during the preceding decade. Most of them consisted of case reports diagnosed either before or after death. There was considerable discussions on the cellular origin and classification of primary neoplasm but the acceptance of a uniform terminology did not occur until the 1940's. Pulmonary physicians, thoracic surgeons, radiologists, pathologists, and public health physicians debated whether the increase in incidence of lung cancer was apparent because of aging of the population and improved diagnosis, or real and absolute because of introduction of occupational and environmental factors since the turn of the century.

Tabulated Case Reports

The headings used in earlier tables (Chapter 2, pages 74-77), are repeated below, including investigator's names, geographical location, gender of patients, occupational and environmental factors and hostal factors influencing predisposition or susceptibility to lung cancer. There were only 12 publications (out of 223) that mentioned smoking habit, indicating that about 5 percent of physicians suspected that there was a causal association. The total patients reported in the following table are as follows: 2632 males, 511 females, 1569 gender not mentioned, a total of 4712 patients with male to female ratio of 5.2 to 1.

Primary Lung Cancer Case Reports

State/Country (Ref.)/Author	Number/ Gender	Occupational Factors	Host Predisposition
Arkansas			
(3512) Matthews	1M		cardiac metastases
California			
(3212) Rogers	39M; 11F	upholsterer domestics	Austrian or Europeans 30 had parents death due to cancer
(3411) Floridis, Nixon & Ginsburg	1M	farmer	American; swollen finger
(3611) Shuman	1M		bronchoscopy
(3913) Dolley & Jones	3M; 3F		X-ray and surgery
(3914) Holman & Pierson	5M; 1F	farmer, hotel clerk molder, housewife tile setter	Japanese, German, X-ray diagnosis
Colorado			
(3412) Bronfin	5M; 1F	house painter, merchant, contractor, hardware merchant	tuberculosis rare bronchoscopy
(3915) Harper	1M		X-ray therapy
District of Columbia			
(3213) Freeman	4M		epileptic, aphasia, psycholic brain metastases
(3413) King	4M*		1 "cigarette cough"
Florida			
(3111) Carrington	1M	farmer, ex-soldier	X-ray therapy
Georgia			
(3011) Bonner	5M; 1F		Jewish male and female, 1 with family history of cancer, 3 without family history of cancer
Hawaii			
(3612) Fennel	2M	cook	Japanese, Filipino
(3814) Strode, Fennel & Burgess	1M		Japanese
(3916) Strode, Fennel & Burgess	same		surgery
Illinois			
(3012) Wells & Cannon	1M		knocked down by car
(3302) Hruby & Sweany	10M; 2F	clerk, 2 housewives 6 indoor laborers, 3 outdoor laborers	3 Teutonic, 5 Slavic, 1 Celtic 3 American born

(3414) Steiner & Francis	2M; 1F	machinist, photographer	1 Italian, 1 Serbian, all apical cancer
(3513) Sweany	1F*		Polish
(3514) Leader	1M	veteran	varicocele, arthritis
(3515) Louis	1M		German, brain metastases
(3516) Jaffe	92M; 8F		20 syphilis, silicosis
Illinois			
(3613) Arkin & Wagner	125M*;10F	90% smokers	
(3712) Jack	4M; 2F	ex-soldier	X-ray classification,
(3815) Stein & Jostin	139M; 25F	farmers, laborers	7 pneumoconiosis, 10 colored, 7 tuberculosis, 6 syphilis
(3816) Volini & Shaporo	10M	steel worker, clerk contractor	
(3813) Adams	2M		surgery
(3818) Stein	7M	postal worker, cook, machinist, salesman, rail agent, chauffeur	6 apical
(3918) Jenkinson & Hunter	19M; 4F		X-ray diagnosis
Iowa			
(3917) Leik	1M		Polish, adult measles
(3713) Scheele	1M		adult mumps
Indiana			
(3415) Gould	1M		10 year old
Kansas			
(3517) Wood, et al	14M; 2F		bronchoscopy
(3819) Welker & Leger	1M		generalized tuberculosis
Kentucky			
(3312) Harding (review)			
(3820) Carman	3M*	farmer	1 cigarette smoker
Louisiana			
(3518) Gorman	2M		X-ray diagnosis
(3919) D'Aunoy et al	68M; 6F		37 squamous cell 21 reserve cell 16 columnar 27 Negro
(3920) Halpert (review)			
Maryland			
(3313) Hamman	7M; 4F	baker, laborer salesman	X-ray diagnosis
(3417) Geschickter & Denison	47M; 5F		34 epidermoid, 18 adenocarcinoma

(3418)	Reinhoff & Broyles	1M		surgery
(3519)	Warner	11M	stone-cutter	syphilis, influenza, arthritis, family history of tuberculosis

Massachusetts

(3013)	Fremont-Smith et al	17M; 1F		diff. tuberculosis
(3014)	Lord & Mallory	1M	school teacher	typhoid fever
(3015)	Thomas & Mallory	1M	cook	pulmonary emphysema
(3033)	Fried & Buckley	11M; 4F	railyard worker seaman, chef	intracranial metastasis, Russian Jew
(3112)	Frothingham	39(? gender)		diff. tuberculosis
(3214)	Young et al	11M	paper hanger	family history of tuberculosis
(3314)	Overholt	1M	minister	surgery
(3419)	Overholt	1F		surgery
(3520)	Overholt	3M; 5F		surgery
(3614)	Overholt	23 (? gender)		surgery
(3714)	Overholt	37 (? gender)		surgery
(3821)	Overholt	22 (? gender)		surgery
(3822)	Overholt (review)			surgery
(3921)	Overholt & Rumel	70 (? gender)		surgery
(3922)	Overholt	1F		surgery, 5 year survival
(3923)	Overholt	12M; 10F		surgery
(3315)	Churchill	3M; 1F		surgery
(3420)	Churchill (review)		tar dust from road	influenza
(3422)	Chapman & Mallory	1M	machinist	tuberculosis
(3421)	Means	1M	tailor	Australian
(3521)	Churchill et al	1M	candy worker	Italian, emphysema
(3522)	Olson	55M; 14F		
(3615)	Churchill (review)			bronchiectasis
(3823)	King (review)			
(3927)	Pettingill			diagnosis

Michigan

(3113)	Allen & Smith	1F		antirabies vaccine
(3423)	Allen	1F		surgery
(3523)	Samson	15M; 4F		
(3524)	Alexander	25 (? gender)		surgery
(3715)	Pierce & Ingersoll	52M; 10F	10 farmers, 9 housewives, 9 merchants, 7 professionals, 23 industry personnel	X-ray diagnosis
(3716)	Leucutia	3M; 3F		radium therapy
(3717)	Brines	69 (? gender)		31 oat cell, 6 adenocarcinoma, 27 squamous cell, 5 combined forms

Minnesota			
(3016) Wittich	1M	pleural effusion	X-ray diagnosis
(3030) Goltz	2M; 1F	printer, housekeeper	X-ray diagnosis
(3017) Colton	1M	waterworks repairman	syphilis
(3114) Kirklin & Ochsner	1F		breast carcinoma
(3115) Simons	1M	sandblaster, fisher 1/2 year, bodyworks	19 year old
(3215) Vinson	57M*;14F	less than half were smokers	8 family history of carcinoma
(3316) Simons (review)			
(3317) Leddy & Vinson (review)			
(3525) Simons (review)			
(3824) Simons (review)			
(3924) Craig et al	3M; 3F	retired contractor cloth merchant, housewives	brain metastases
Missouri			
(3018) Rabinovith & Harms			rheumatic fever, tuberculosis
(3318) Carlson & Ballon	21M; 5F		surgery
(3424) Tuttle & Womack	150 (? gender)		surgery
(3616) Glenn (review)			
(3617) Graham (review)			
(3319) Graham & Singer	1M	physician	first successful surgery
(3925) Graham (review)			
(3926) Lockwood	3M		diff. tuberculosis
Nebraska			
(3526) Neely	80 (2.8M:1.8F)		5 tuberculosis
New Jersey			
(3116) Polevski	5M; 1F	carpenter, fireman,	1 mustard gas (France)
(3527) Orton	18M; 3F	rail worker, clerk, real estate broker, printer, engineer	bronchoscopy
(3528) Klein	3M*	1 cigarette smoker	X-ray diagnosis
(3529) Fine & Jaso	1M*	pipe smoker	silicosis
New York			
(2629) Cave	4M	newspaper editor	tuberculosis
(3019) Miller & Jones	24M; 8F	11 outdoor workers	5 Russian
(3020) Rosahn (review)		12 outdoor workers	1 Jew
(3021) Von Glahn	5M; 1F		tuberculosis
(3122) Sharp	3M	machinist	bronchoscopic aspiration
(3022) Torek	1F		metastases from uterus
(3117) Moses	8M; 3F		
(3216) Moses	3M; 2F		polyps turned malignant
(3217) Wessler & Rabin	9M; 8F		
(3218) Williams	1M	plumber	
(3320) Neuhof	3M; 2F		surgery

(3321)	Lilienthal	1F		surgery, tuberculosis
(3322)	Lloyd	1M		surgery
(3323)	Kernan & Cracovaner	1M	carpenter	emphysema
(3425)	Hirsch	1F		bone metastases
(3426)	Eggers	1F		surgery
(3427)	Crowell	1M	textile foreman	pleural effusion
(3428)	Rabin & Neuhof	100 (? gender)		circumscribed and non-circumscribed types
(3429)	Klinck & Jacobson	2M		psychosis
(3441)	Fried	2M	leather operator, carpenter	X-ray treatment
(3530)	Andrus	117 (? gender)		tumor registry
(3531)	Frissell	28M; 10F		
(3543)	Saccone & Handler	10M		cerebral metastases
(3618)	Graef & Steinberg	1M	salesman	apical tumor
(3619)	Lyle	1F		surgery
(3620)	Kramer & Som	300 (? gender)		bronchoscopy
(3621)	Rosedale & McKay	52M; 5F	14 no irritating hazard, 43 irritating hazard	bronchoscopy
(3631)	Ehrlich & Hauptman	107M*;17F	10 housewives, 1 war gas, 10 laborers, 8 carpenters, 1 drug addict, 9 tailors, 1 heavy smoker	
(3705)	Frissell & Knox	10M; 36F		
(3718)	Craver	1F		X-ray therapy
(3719)	Mattick & Burke	62M; 11F		X-ray diagnosis
(3825)	McGaback	75M*;15F	14 heavy smokers 60 heavy and light smoker	25 fibrosis 18 abscess
(3929)	Hochberg & Lederer	47M; 13F	trader, clerk, cloth presser, builder, cloth operator	
(3928)	Craver & Binkley	67 (? gender)		aspiration biopsy
(3930)	Howes & Schenck	7M; 1F		7 white, 1 Negro 1 tuberculosis
(3934)	Charache	1M		Italian, subcutaneous metastases
Ohio				
(3023)	Karsner & Saphir	4M; 2F		1 Negro, 6 small cell
(3622)	Frost & Wolpaw	1M		syhpilis, apical tumor
(3720)	Bliss	1M	chemist	mother died of cancer bronchorrhea
(3826)	Koletsky	87M; 10F		35 small cell, 22 adenocarcinoma, 40 squamous
(3931)	Gebauer (review)			bronchoscopy

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(3932) Freedlander & Wolpaw	3M; 1F		thoracotomy
Oregon			
(3119) Menne et al	15M; 1F		10 hilar nodular 6 diffuse necrolic
(3827) Matson et al	1M	copper miner	Serbian
Pennsylvania			
(3024) Funk	50M; 11F		diff. diagnosis
(3234) Pancoast et al	2M; 1F		radon implant
(3242) Pancoast sulcus syndrome	5M; 2F		superior pulmonary
(3219) Manges	50M; 11F		X-ray therapy
(3324) Bradshaw	4 (? gender)		treatment
(3325) Clerf & Crawford	48M; 2F		34 squamous cell 2 adenocarcinoma 14 undifferentiated
(3721) Clerf	143 (? gender)		bronchoscopy
(3623) Marcil & Crawford	1M	salesman	apical tumor
(3624) Flick & Gibbon	1M		surgery
(3829) Flick & Bauer	12 (? gender)		surgery
(3722) Charr	4M	coal miners	anthracosilicosis
(3723) Farrell	45M; 5F		23 squamous cell 3 adenocarcinoma 24 undifferentiated
(3830) Bauer	30M*; 2F	15 of 32 smokers	1 kicked by a horse 1 struck by a truck
(3831) Warmolts	10M	navy personnel	
(3933) Behrend & Behrend	2M	plumber	surgery
Rhode Island			
(3326) Beardsley	1F	16 months old	adenocarcinoma
South Carolina			
(3532) Smith	4M; 1F	cotton mill weaver	asbestosis
Tennessee			
(3533) Heacock & King	20M; 5F		bronchoscopy
Texas			
(3327) Pilcher & Brindley	8M; 1F	oil field laborer, carpenter, baker, cook, peddler	3 tuberculosis
Virginia			
(3625) Nelson	2M	farmer, cabinet maker, insurance-man, roofer, sea-man, all cigarette smokers	tuberculosis
(3833) Faget & Harmos	5M*		chest injury

(3834) Vinson (review)			carcinoid
Wisconsin			
(3416) Jermain	1M	foreigner	bone metastases
(3626) Rice	18M; 12F	4 farmers, 3 metal workers, 4 laborers, 8 housewives	influenza
Australia			
(3220) Duhig		boat maker, office caretaker	
(3328) Gutteridge	27M; 1F		surgery
(3430) Maxwell	1M	goldminer	silicosis
(3835) Turner & Willis	1M	tin miner	back trauma
(3836) Shaw	7M; 1F		bronchoscopy
Austria			
(3627) Fleckseder	54M*; 8F	12 outdoor workers 28 indoor workers	51 smokers
Canada			
(3025) Paterson (review)			
(3026) Boyd (review)			
(3027) Hodge	1M	coal miner	anthracosis
(3431) Meakins (review)			
Argentina			
(4002) Palacio & Mazzei	100M;12F		translation needed ?
Denmark			
(3724) Husted & Billmann	41 (? gender)		2 chronic lung disease
France			
(2802) Huguenin	44 (? gender)		translation needed
(3725) Ameuille & Fauvet	2 (? gender)		
(3703) Soliman	29M; 4F		translation needed
Great Britain			
(2630) Barnard (review)			oat-cell carcinoma
(3003) Davidson	19M; 4F	box collector, publican, chauffer, toolmaker, carpenter, retired army officer	
(3037) Maxwell & Nicholson	83M; 17F	34 outdoor workers 86 indoor workers	bronchoscopy
(3120) Edwards	2M; 2F		radon therapy
(3432) Edwards	53M; 20F		radon therapy
(3433) Edwards (review)			
(3434) Edwards	1M; 1F		radon therapy

(3435) Edwards (review)			
(3602) Edwards (review)			
(3838) Edwards (review)			
(3121) Peet	56M; 10F	30% coal miners 17% industry laborers	
(3221) Kerley (review)			x-ray diagnosis
(3222) Brockbank	52M*;10F	18 gas and fumes, 9 dusty jobs, 13 non-smokers, 9 smoked twist, 9 heavy smokers	4 war gas
(3534) Dudgeon & Wrigley	53 (? gender)		sputum wet film
(3329) Roberts	9M	tobacconist, carter carman, roadman, laboratory techncian	X-ray treatment
(3436) Dible	3M; 1F	3 stone mason 1 soapstone worker	silicosis
(3446) Ellis	4M; 1F	laborer, carter mason	cocaine and morphine treatment
(3437) Hill (review)			
(3438) Sears	23M; 3F		cocaine treatment
(3439) Young	1M	caisson sinker	surgery
(3440) Scadding	1M		radon treatment
(3535) Matheson	1M	carman	pericardial metastasis
(3628) Wood	13M; 1F		surgery
(3629) Holmes	4M; 1F		diagnosis
(3635) Bush	6 (? gender)		X-ray
(3630) El Gazayerli	79M; 16F		66 oat cell, 28 adeno-carcinoma or squamous
(3726) Tchaperoff	41M; 5F		X-ray treatment
(3727) Ormerod	92M; 8F		62 squamous cell 38 nonsquamous
(3728) Craig	3M; 1F		osteoarthropathy
(3729) Alexander	1M	transport driver's mate	19 year old oat cell
(3839) Allison & & Stanbury	2M	miner	surgery
(3840) Barrett	110 (? gender)		37 sputum positive 31 sputum negative
(3841) Brock (review)			surgery
(3842) Owen et al	5M; 2F	railway checker, tram driver, carpark attendant, butcher, forwarding clerk	apical tumor
(3843) Pilcher (review)			
(3844) Pilcher (review)			
Italy			
(3536) Becchini	10M; 1F		translation needed ?
(3103) Verga & Botteri	22M; 8F		translation needed ?

Sweden (3837) Westermark	55 (? gender)	X-ray patterns	

* Tobacco Use

The articles indentified as Review are on the following subjects: diagnosis by symptomatology, radiology, bronchoscopy, clinical management, surgical treatment and microscopic features of lung cancer.

Apparent and Absolute Increase in Lung Cancer?

During the 1930's, proponents of causal association relied on the coincidental increases in male lung cancer incidence and in male smoking prevalence. Harris based his opinion on his interpretation of the literature:

> "5.1. During the period prior to World War I, pathologists, clinicians and vital statisticians began to note an increase in lung cancer - a disease that was relatively obscure prior to 1900. By the late 1920s and 1930s, a dramatic increase in primary lung cancer, predominantly among males, was recognized throughout the United States and Europe. Lung cancer began to overtake cancer of the stomach in clinical and autopsy series and in vital statistics analyses.
>
> 5.2. At the start, there was controversy concerning the genuineness of the increase in lung cancer incidence. Alternative explanations emphasized improved methods of diagnosis, increased autopsy rates, population aging, changes in disease classification and generally enhanced cancer awareness among physicians. However, such explanations did not accord with other facts, including the increase in the age-specific incidence of lung cancer, the disproportionate rise in lung cancer among males, the rise in lung cancer relative to cancers of other internal organs, and the increased proportion of lung cancers seen at autopsy. Beginning in the late 1920s, a growing number of pathologists, surgeons, vital statisticians, and other scientists realized that, at least since 1920, the rise in lung cancer was genuine, both relatively and absolutely.

During the deposition, Counsel selected the phrase "disproportionate rise in lung cancer among males" for clarification, using the complex and long 1936 article by Kennaway and Kennaway. A simplier approach was to have gone one

step backward and challenge whether "the rise in lung cancer was genuine both relatively and absolutely."

Harris used the following articles to support the above summary statements: Perret (2711), Hoffman (2911),(3131), Mertens (3031), Arkin & Wagner (3613), and Kennaway & Kennaway (3632). These articles discussed under Topics C, D, and E, contain statements that question Harris' interpretation. Other Harris' references for his statement 5.2 are discussed in Chapters 4 and 5: Müller 1939, Ochsner & DeBakey 1939, 1941, Menne & Anderson 1941, and Graham 1951. In addition to the above references cited by Harris in his SOA 5.2, there are two comprehensive reviews missed by Harris. Simons, in his monograph entitled Primary Carcinoma of the Lung, stated:

> "It is apparent that the evidence permits of no other conclusions than these: first, that incidence of the disease has increased both absolutely and relatively; second, that continued suggestions that such an increase in only apparent and not real are rebuked by the facts; third, that the increase was gradual until the early 1900's, since when the gradient of increase has become constantly steeper; finally, that in many localities the greatest incidence seems to have been reached in 1924, while in others the frequency still is advancing." (pages 50-51 of ref. 3702)

Rosahn, in his 1930 review article entitled "The Incidence of Primary Carcinoma of the Lung", wrote the following:

> The postmortem incidence of primary carcinoma of the lung is steadily increasing, and this increase is real and absolute. Combined statistics show that primary carcinoma of the lung at autopsy from 1910 to 1919 comprised 0.44 per cent of autopsies, and 4.39 percent of all cancers. Since 1920, primary carcinoma of the lung at autopsy comprised 0.89 per cent of autopsies and 6.98 per cent of all cancers. Primary carcinoma of the lung is not as rare as was formerly believed. (pages 809-810 of ref. 3020)

The two reviews generally agree with Harris' interpretation. However, British and American authorities question interpretation of Simons and Harris.

British authors who question "absolute increase".

The situation during the 1920's and 1930's was confusing because an increase in incidence, whether relative or absolute, was denied by Passey and Holmes (3537) and Bonser (2845, 3458) from the University of Leeds. Davidson, from Brompton Hospital, detected an increase but was preoccupied with comparison to German statistics instead of analyzing whether the increase was relative or absolute (3003). Kennaway & Kennway (3632) compared the incidence of lung cancer with those of prostatic cancer reported by Moore (3538). They also discussed the possible factors which might have caused increase in lung cancer deaths:

> The increase in recent years in the number of deaths attributed to cancer of the lung may be due to one, or more than one, of the following factors: (1) An increase in the actual number of cases of the disease; (2) Improvement in diagnosis, whereby a larger proportion of the actual number of cases is detected in life; and an increase in the number of autopsies performed; (3) A tendency to identify as cancer of the lung cases which are really of a different nature; that is, a fashion in diagnosis. These three possibilities may now be considered in detail.
>
> (1) An actual increase. It is obviously difficult to obtain any direct evidence of this factor; one is driven to seek for indirect evidence by means of enquiry, how far the second and third factors can be excluded. The actual number of cases of any form of cancer must depend upon the size of the population of the country, and upon the distribution of age and sex within this population. But the increase in recorded cases of cancer of the lung is too great to be accounted for by any such influences. The dissemintion of tar from roads has been thought to be a factor which must produce an increase in cancer of the lung.
>
> (2) Improvement in diagnosis. The methods of examination of the lungs, and the provision of apparatus for such purposes, have undergone very great development in the last fifteen years, and it would be remarkable if these changes had not increased the number of cases of cancer of the lung detected. Hence there can be no doubt that this accounts in part for the apparent increase in the prevalence of cancer of the lung, but the question remains,

whether a real increase is occurring also. If improvement in diagnosis is the whole explanation of the sharply rising curve in Graph 2 then over 1000 deaths from cancer of the lung in men in 1930 must have been ascribed to other diseases (see the figures for 1930 (1056 deaths) and for 1934 (2095 deaths) in Table XII. Obviously this factor will cease to act when the methods of diagnosis, and their availability to the whole population, cease to improve; hence it will be of great interest to see the changes in the prevalence of cancer of the lung in, say, the next 10 years.

A comparison of the prostate with the lung in this respect is of interest. Cancer of the prostate has shown a rate of apparent increase (Graph 4) which is very similar to that of cancer of the lung in males. The graph shows the recorded deaths from these two forms of cancer in England and Wales for the 24 years 1911-34. The number of cases of cancer of the lung remains at a very constant level of about 250 during the period 1911-19, and then shows a rise of increasing steepness to more than eight times that figure, or 2095, in 1934. The deaths from cancer of the prostate show a more uniform increase, though here again there is a tendency for a more rapid rise to set in during 1918-20; the last figures available, namely those for 1932-3-4 (Table XIV) indicate that the increase is coming to an end.

Recent investigations have shown that areas of tissue regarded as malignant can be found at autopsy in a high proportion of prostates, if a sufficiently minute search be made. There is thus in the case of the prostate a reservoir of malignancy which is drawn upon in proportion to the thoroughness of the examination, and it is probable that the same is true of the lung.

Passey and Holmes (3537) in an elaborate study for the years 1894-1928 of the numbers of intrathoracic neoplasms in relation to admissions to sixteen hospitals, found an increase in such tumours in five hospitals only of the sixteen, and these authors conclude that the reader 'will find it difficult to make out a serious case for any appreciable increase in the incidence of intrathoracic neoplasia in the period 1894-1928 ...'. This may be so, but it is difficult to see why the recent great increase in certification of deaths from cancer of the lung did not take effect upon more of the hospitals dealt with by Passey and Holmes, for one cannot suppose that the diagnoses in these institutions in, say, 1919, left no room for improvement.

(3) Fashion in diagnosis. The suggestion has been made that there is now a tendency to identify as cancer of the lung cases which are really of a different nature. If this factor is to account for the present form of the curve (Graph 2) one must suppose that every year medical men diagnose two or three hundred more cases wrongly; it will be interesting to see for how many years this course of action persists so as to maintain the curve

> in its recent shape. Also, there must be a sufficient supply of patients who have intrathoracic conditions which are not cancer of the lung but are sufficiently severe to cause death. It seems very unlikely that this third factor can have any large influence upon the figures in question." (pages 255-257 of ref. 3632)

Since the existence of an increase in both males and females was uncertain, it was more difficult to analyze comparative increases in males and females. It was therefore not surprising that Harris' deposition relating to Kennaway & Kennaway appeared to be frustrating for both parties (DTH 607, Exhibit 62; SOA 131; Exhibit P131). In the Transcript of Proceeding, Harris was questioned about the contents of article by Kennaway & Kennaway (pages 1566-1567). The line of questioning was <u>percentage</u> increases in males compared to females, which to Harris "in percentage terms, what that meant when I read it, I was never sure."

<u>American authors who question "reality of increase in lung cancer incidence"</u>.

During the 1930's, several American monographers concluded that the statistics <u>did not</u> support the concept that there was a real and absolute increase in incidence of lung cancer. Instead, they proposed that there was a relative increase as a result of several factors that are described in the following quotations by Monographer (k) Fried, an internist from Minnesota:

> "The lack in the past, of knowledge of this condition, plus the unreliability of cancer statistics in general, considerably weakens the statement that bronchiogenic cancer occurs now more frequently than formerly. However that may be, as the problem stands, this point is apparently not susceptible of proof one way or another, and, therefore, no sweeping conclusions should be drawn.
>
> The author is of the opinion that the more frequent occurrence of this disease in recent years, as compard with older findings, can be explained on the basis of the following factors: (1) Improved clinical and pathological methods of diagnosis; (2) Increased attention to this malady (as Goethe has expressed it:

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> Man sieht nur was man weiss"); (3) Increase in span of human life (a much greater proportion of people reach the 'cancer age'). The increase, then, is very likely more apparent than real. (page 13, ref. 3201)

Additional quotations from Fried are included under Topics C and D. The opinions of other internists are in the next paragraphs.

Monographers (d) Hruby and Sweaney, in their review entitled "Primary Carcinoma of the Lung with special reference to incidence, early diagnosis and treatment", recalled the following figures:

> In all there are 1,355 cancers of the lung and 22,712 cancers in 185,434 autopsies. By adding the redistributed figures of Junghanns, Probst, Holzer, Derischanoff and Zacherl, who gave the numbers in five year periods, the results were almost identical, giving a total of 2,359 cancers of the lung and 38,338 cancers in 359,389 autopsies, perhaps half of all cancers of the lung reported to date.
>
> These figures and charts reveal a gradually increasing incidence of general cancer of around 65 per cent over the thirty-four years with a depression during and after the war. There is also an increasing incidence of cancer of the lung that is greater than the incidence of general cancer until the war; then, after a slight depression, there is a tremendous rise, the peak being reached in 1928, amounting to a tenfold increase. Since then there has been a tendency to decrease. Corresponding to this rise, however, is an increase in the diagnoses of cancer of the lung, as given by certain authors, from 5 per cent in 1896 to about 50 per cent in 1925. With careful work, it should approach 75 per cent at the present time. General cancer is entirely different. The diagnosis in this group should have been well over half correct throughout the whole thirty-four year period. Instead of a tenfold increase in diagnoses, as with cancer of the lung, there is no more than a 10 or 15 per cent increase.
>
> It may be contended that an increase in diagnoses should have no effect on figures based on autopsies, but it will tend to bring more cancers of the lung to autopsy and to increase the figures based on autopsies at the expense of the greater group of cancers of the lung that do not come to autopsy. Furthermore, the tendency to more hospitalization, better transportation, better training of physicians during the war and a better appreciation of medical aid on the part of the returned soldiers will increase the recorded incidence without affecting the true incidence of cancer of the lung.

The causes of the increase in diagnosis of cancer of the lung are many and variable. In this regard, one must bear in mind that the discovery of the tubercle bacillus in 1882 permitted a vast number of patients to be separated from those definitely tuberculous and has made further search of diagnosis necessary. It has been our observation that tubercle bacilli are found in all but a trivial minority of active, advanced cases of pulmonary tuberculosis.

The discovery of the x-rays in 1896, with their far-reaching application in medical diagnosis in the last twenty years, has also established the diagnosis of cancer of the lung in many patients whose disease would otherwise have been classed as some other condition.

The use of opaque substances (iodized poppy seed oil 40 per cent), bronchoscopy, pneumothorax, thoracoscopy and bronchoscopic section have all added to diagnostic equipment until over 75 per cent of the diagnoses of cancer of the lung today are, or should be, correct, while less than a decade ago Staehelin, Kikuth, Wells, Grove and Kramer and others reported not over 35 per cent correct diagnoses. Ferenczy and Matolcsy reported 5 per cent correct diagnoses from 1896 to 1900, 28.4 per cent from 1917 to 1925, and 50 per cent in 1925. In Lubarsch's series, the correct diagnoses totaled 52 per cent in 1920. In 1913, Weller reported only 11 per cent in a collected series of 90 cases. These figures show a marked improvement in diagnosis as years go by.

This same principle applies to nearly all internal and 'inaccessible' cancers, although the incidence of external cancers has changed little - in fact, the death rate from external cancer has decreased.

More important than any other factors, however, is the change in pathologic diagnoses. Pathologist have varied their attitude toward the nature of cancer of the lung, thereby placing many cases in this group that were formerly considered to be some other condition. As pointed out by Fried (3201), a dictum of Virchow pervaded the field for a long time. Virchow was of the opinion that the tissue which was subject to metastatic growth rarely produced primary growth, and the lungs were cited as an example. Only a few scattering reports came from the early writers, and perhaps not until Virchow's great influence began to wane did the subject again become open to unbiased investigation. Many of the cancers found in the lungs were formerly considered to be metastases because they are chiefly located at the hilus, where metastases commonly occur. Many were also considered as mediastinal tumors.

One of the greatest changes, however, from the pathologists' point of view, was due to a better understanding of the origin of the undifferentiated cells in cancer of the lung, many of which were formerly considered sarcomatous.

> Some of the small cell and even the 'oat cell' types may have been considered as sarcomas. In Hunt's series of 26 cases, 21 were of the 'oat cell' type. Then many were perhaps considered mediastinal tumors (lymphosarcomas, thymomas and similar tumors) without careful histopathologic analysis. So one sees that it is not only an improvement in diagnoses but the change of erroneous diagnoses in a relatively small group of cases that come to autopsy that may well have produced a tremendous change in the apparent incidence of cancer of the lung." (pages 504-506 of ref. 3302)

The data cited above were derived mostly from German publications and compared with American and British statistics. The overall interpretation by Hruby & Sweaney is that this increasing incidence was due to improved diagnosis.

Monographers (f) Frissell & Knox, in their 1937 article entitled Primary Carcinoma of the Lung stated:

> It is obvious, then, that primary carcinoma of the lung is not the rare disease it was formerly believed to be, but the question as to whether the increase is actual or apparent is still open to debate. The following observations must be taken into account. First, many tumors classified as sarcomata by pathologists of the last century are now included as epithelial tumors of the so-called oat-cell variety. Secondly, carcinoma of the lung, when found, was usually considered metastatic; this resting on the statement of no less an authority than Virchow, who stated that organs in which epithelial tumors metastasized were rarely the seats of primary carcinoma. Third, the widespread interest of pathologists in this subject, particularly in the last decade, has led to the discovery of a considerable number of small pulmonary neoplasms with large metastases; such metastases earlier observers undoubtedly regarded as the primary lesion. Clinically, there is no question that our newer methods of investigation - roentgenography with or without lipiodol, bronchoscopy, thoracoscopy, etc. - have led to frequent ante-mortem diagnoses, whereas in the early literature the diagnoses were almost exclusively post-mortem. Since external and readily diagnosed cancer has not increased, it would seem probable that, in spite of the evidence of the post-mortem figures, especially in Germany, the increase in the incidence of bronchial carcinoma in the last two decades is apparent rather than real. Our own statistics seem to agree with the other in indicating a general rise, whether or not it be an actual one. (page 220 of ref. 3705)

The above quotations are repetitive but are useful in emphasizing that the claim of an absolute increase in lung cancer incidence was questioned by American physicians.

Monographer (g) Klotz represented the opinion of some pathologists that interpret the increase incidence as apparent rather than real or absolute:

> "Nearly all are agreed that the condition is encountered with greatly increased frequency, and this has raised the controversial question of whether the increase is actual or apparent. In a survey of much of the European literature on the subject, Bonser found a reported increase in the condition in 32 instances, a slight increase in 5 and no increase in only 8. Wahl from 1895 to 1927, found an increase in the incidence of cancer of the lung from 0.44 to 1.69% of all autopsies; Duguid, from 1885 to 1926, observed an increase from 0.24 to 2.57%; Kikuth, from 1889 to 1923, showed an increase from 0.02 to 0.86% and Barron, from 1889 to 1921, an increase from 0 to 0.9% and so on. The increased frequency with which the disease is recognized is further emphasized when one considers that Adler (1201), was able to collect but 374 authenticated cases, whereas a complete present-day summation would number thousand with some reports, including a hundred or more from a single source. A few investigators believe that no increase has occurred in the incidence of carcinoma of the lung. Thus, Bonser (3458) was unable to demonstrate any change in the incidence of the condition in relation to total autopsies, total cancers, or hospital admissions at the Leeds Infirmary. Though this worker did observe that the highest incidence occurred durng the 5-year period ending in 1932, this was only slightly in excess of the incidence for the 5 years from 1908 to 1912. Similarly, Passey and Holmes (3537), in a carefully controlled analysis of the available statistics from some of the teaching hospitals of Great Britain, found no increase in the incidence of carcinoma of the lung in 8 instances and a variable increase in 8 others. These writers considered that the increased incidence found in these latter was the result of special circumstances and did not indicate a real change. The statistics from several of these hospitals, from which it was deduced that no increase had occurred, had previously been reported in a different form and had been considered indicative of an actual increase.
>
> Despite such reports as the foregoing, the great majority of authors are agreed that the condition is now seen more commonly than formerly. Most of them, however, consider the increase purely apparent and offer a variety of reasons in explanation of this. Important among these are the increased span of human life, and increased interest in the condition stimulated by both improved diagnostic equipment and the hope of carrying out

> successful intrathoracic surgical procedures. Other important factors are fashion in diagnosis, and the changed attitude of the pathologist who now recognizes to be actually primary carcinoma pulmonary lesions formerly considered metastatic, sarcomatous or inflammatory." (page 440 of ref. 3802)

William Boyd, prior to writing a Textbook of Pathology, published an articled entitled "Some Reasons for the Recent Increase of Bronchial Carcinoma":

> "Let us now retrace briefly the steps that we have taken in our inquiry. We have seen that there are a number of factors each of which has contributed in turn to the sum total of cases of bronchial carcinoma which are recognized at the present day. Of these by far the most important is the truth contained in the saying: 'What we know, we see'. That is true of coronary thrombosis and it is true of bronchial carcinoma. It is true, moreover, for the clinician, the bronchoscopist, the radiologist, and the pathologist. The eyes of the first three have been opened by the observations of the pathologist. The pathologist's myopia is the most difficult to explain. It may be accounted for in three ways. (1) The gross lesion may closely resemble other neoplasms or may be obscured by changes secondary to bronchial obstruction. (2) Recent years have brought realization of the fact that carcinomas in general and those of the bronchus in particular vary greatly in their microscopic appearance and may closely mimic sarcomas and lymphosarcomas in this respect, so that even the microscope may fail to correct the error. (3) The natural history of the disease as illustrated by the behavior of metastases is highly characteristic, but the knowledge of this truth is of recent date. Without denying the possibility that there may be some real increase in the incidence of the disease, it is suggested that the various factors which have been discussed, coupled with the present increase in the span of life, are sufficient explanation for the apparent increase which has attracted the attention of observers in all countries - observers, however, who have had their eyes opened so that they can look-see as well as look, and who therefore see what they know." (pages 329-320 of ref. 3812)

The above comments by Boyd are essentially similar to an earlier article (3026). His opinion is unlike that of Ewing, another pathologist.

Although surgeons are presently against cigarette smoking, it is important to note that their publications in the 1930's did not reflect an

anti-smoking attitude. Graham, Singer and Ballon, in their monograph entitled Surgical Diseases of the Chest, stated:

"Statistics. - There are many who are of the opinion that carcinoma of the lung is definitely on the increase. The following statistics reported by others are, therefore, presented in an attempt to see if the increase is definite or merely relative. M. Brandt (Riga) reports findigs in 13,179 necrospsies performed between the years 1901 and 1925. There were 828 cancers, 108 were primary in the lung. Between the years 1901 and 1905 the pulmonary cancers comprised 1 to 2 per cent of all tumors. Between the years 1916 and 1921 and 1925, pulmonary cancers comprised 10 to 11 per cent of all the cancers.

S. Wahl has reported the following statistics from the Municipal Hospital Moabit. During the years 1922 to 1927 there were 3372 autopsies. There were 57 cancers which were primary in the lung or 13 per cent of the cancers observed (438); during the years 1916 to 1922 there were 3342 necropsies, 396 cancers, 24 of which were primary in the lung (6.06 per cent).

Hanf, of the Charite, Berlin, has published (1903 to 1925) the statistics shown in Table 106.

Holzer of Prague has reported some statistics on cancer of the lung over the years 1895 to 1924. During the first ten years primary cancers of the lung comprised 1.04 per cent of all cancer, during the second decade 2.36 percent and during the third decade 6.69 per cent. There were more necropsies in later years and consequently more primary carcinomas of the lung, still the increase in primary lung tumors was apparent.

de Vries reported 39 carcinomas of the lung observed in 8000 necropsies. Twenty of these were seen during the period of 1922 to 1926.

Frenczy and Matolecsy of Vienna have reported most instructive statistics. Since 1925 there were 2,821 postmortems; 334 tumors, 24 primary in the lung or 7.2 per cent.

v. Zalka in 1928 published statistics from St. Stephens Hospital, Budapest, from 1894 to 1927. They showed that since 1904 the percentage of lung cancers relative to all cancers has varied very slightly. The maximum occurred between 1914 and 1918 (3.35 per cent). From 1919 to 1923 it was 2.67 per cent and between 1924 and 1927 the proportion has increased to 6.65 per cent.

The incidence of primary carcinoma of the lung is given by Weller who states that prior to 1900 the percentage of incidence of carcinoma of the lung at autopsy ranged between 0.57 per cent (Reinhard) and 0.428 (Wolf). The statistics compiled by Brunn are given in Table 109.

Reference has already been made to the increase in incidence of carcinoma of the lung in particular institutions. The reasons given for this increase are better methods of diagnosis, more correct diagnoses, recommendations of more such patients to the

hospital, actual increase, etc. These various factors will be referred to again.

In reporting some interesting statistics on cancer Hoffmann (3131) has made reference to the reports published by the Census Office of the United States. In 1914 out of 52,420 deaths from all forms of cancer 371 were attributed in this report to cancer of the lungs and pleura. The equivalent proportion was 0.7 per cent but at a rate of 0.6 per 100,000 of population. Ten years later, 1924, the number of recorded deaths from cancer of the lungs and pleura was 1586 equivalent to 1.7 per cent but at a rate of 1.6 per 100,000 population. Statistics for England and Wales for carcinoma of the lung and pleura during 1901 to 1910 was 1 per 100,000 of standardized population. From 1911 to 1920 the corresponding death-rate was 1.34; during the year 1926 it had reached 2.33. For Albany, New York, the rate for cancer of the lung for 1919-1923 was 2.5. For New Orleans during the same period it was 2.8 for white population and 0.6 for the colored. For Chicago it was 2.8 for 1924 and 2 for 1925. For British Columbia it was 2.1 for 1920 to 1924; for Saskatchewan during the same period it was 9.5, for the city of Winnepeg 3.3. Hoffmann was unable to find a single case which could be attributed to nicotine. (pages 808-811 of ref. 3502)

Graham, in his 1936 article entitled "Primary Carcinoma of the Lung or Bronchus", stated:

"One of the most discouraging results from the study of any large series of cases is the revelation that nearly all of them have been allowed to progress to an advanced state without so much as a suspicion in the doctors' minds of the true nature of the condition. One can forgive an attending physician for not establishing the diagnosis of bronchiogenic carcinoma because of the expert teamwork that is sometimes necessary. It seems difficult, however, to excuse him when he does not even take the possibility into consideration in a case of unexplained cough which has arisen insidiously in a patient of middle age or older. If the medical profession, as a whole, should appreciate the frequency of this condition, and the necessity and the desirability of taking prompt measures to establish the diagnosis in a suspicious case, probably a great many of the patients might be saved. It is a matter of the greatest importance that educational campaigns should be conducted to inform the general medical profession of the principal signs and symptoms suspicious of this condition and to get them to appreciate that bronchiogenic carcinoma is so frequent that its possibility must always be considered when dealing with a patient with unexplained cough.

The change in the point of view of the profession concerning this condition is well illustrated in a recent experience of ours. From one small city of approximately 100,000 inhabitants not far

increase in cancer incidence (3911). It is apparent that during the 1930's, the increased incidence was being questioned by Americans and Britishers, because the absolute increase was limited to the European continent.

Surgery of Lung Cancer.

One of the most significant development in lung cancer during the 1930's was the progress in surgical removal of the lesion. The first successful removal of an entire lung with bronchial carcinoma was reported in 1933 by Graham and Singer (3319). Graham's publication (3617) and his monograph (3502) are discussed above, and his later publications are reviewed in Chapters IV and V. There was no statement in the 1930's that Graham suspected tobacco smoking as a cause of lung cancer. His accomplishments were the subject of an editorial of the Journal of Missouri State Medical Association (3442). Churchill, Overholt and colleagues, attracted surgical residents to Boston which soon became a center for pulmonary surgery (3314, 3315, 3419, 3420, 3520, 3521, 3614, 3615, 3714, 3821, 3822, 3921, 3922, 3923).

Reinhoff and his collaborators at Johns Hopkins Hospital improved further on the surgical treatment of lung carcinoma (3418, 3633, 3634, 3935, 3949). They developed a two-staged operation for pneumonectomy which did not become popular because of successful one-stage lobectomy introduced from Great Britain (3439, 3841). Dolley and Jones wrote a comprehensive review of lobectomy (3936). I examined most references and could not find any secondary citations used by Harris in support of his concept that cigarette smoking was a cause of lung cancer during the 1930's. In other words, chest surgeons, like Graham,

were not convinced that most of their lung cancer patients were also cigarette smokers (3553).

Bronchoscopy.

Jackson and Jackson from Temple University in Philadelphia improved on the visualization of bronchial passages by endoscopy. They introduced the instruments for direct bronchoscopy that contributed to early detection of bronchial carcinoma (3028, 3443, 3937). There was no mention of cigarette smoke as a cause of bronchial carcinoma. In their monograph entitled Cancer of the Larynx, the chapter on etiology listed 27 causes of laryngeal diseases, including alcohol, tobacco, dust, war gasses and other vapors. The pertinent paragraphs were as follows:

> "Tobacco. - Contrary to that of alcohol the effect of tobacco in producing chronic disease of the larynx is local not systemic. It is not the nicotine but the empyreumatic oil produced by the destructive distillation of the burning tobacco that causes the injury to the laryngeal mucosa. This injurious effect is not confined to the smoker himself but is noticeable in the larynx of anyone who remains long in a room whose atmosphere is saturated with tobacco smoke. Chewing tobacco, which used to be so common, is little if at all injurious locally; if injurious at all it is only by the effect on the general health. Tobacco smoking is one of the chief reasons for the enormous preponderance of men as compared to women afflicted with chronic laryngitis. Since the vice is becoming more prevalent among women this sexual difference in incidence may be lessened. Tobacco smoking is probably one of the minor causes of cancer of the larynx; it cannot be regarded as an essential cause.
>
> Alcohol. - As a clinical fact it has long been known that alcohol is a potent cause of laryngeal disease acute and chronic. It seems to be the impression that local irritation of alcoholic contact is the mechanism. This is a mistake; alcoholic beverages do not reach the larynx. Observation in thousands of patients justifies our opinion that it is the prolonged, peripheral, vaso-dilator effect of alcohol that is so injurious to the laryngeal mucosa. The mucosa of the larynx of the victim of alcohol, who used to be so common before the days of prohibition, was always engorged. It was evidently the chronic engorgment of the cords

> that was responsible for the hoarseness. The engorgement is noted within twenty mintues of the taking of a single drink of whiskey, but if not repeated the engorgement subsides within a few hours. It is the constant repetition of the alcohol that results in the vasomotor condition resembling paralysis and the chronic engorgement. This 'whiskey voice' is a form of hoarseness that disappeared from the United States during the prohibition period. At the present rate of advertising of the liquor interest and the hotels and restaurants, the development of a new group of addicts to the vice of chronic alcoholism is only a question of time. Those who prided themselves on the art of dining, which meant a different wine between each course, had the 'whiskey throat'. It is possible also that 50 per cent alcohol as in undiluted whiskey or brandy in passing over the extrinsic laryngeal mucosa may cause some congestion of this area that might extend to the upper posterior intrinsic area. Dilution of alcohol hastens the vasodilator effect. Total abstinence offers the only hope of retaining a normal laryngeal mucosa. Singers should be warned of this." (pages 51-53 of ref. 3704)

The above quotations appeared in the 1937 Edition of the Jackson & Jackson monograph. The 1939 Edition cited as Exhibit P385 by Harris is not available in New Jersey at the time of preparation of this chapter. Ms. Thompson will compare the above with Chapters XXIII and XXIV mentioned by Harris.

Cellular Origin of Malignancy and Classification.

Although several systems of classifying lung cancer were introduced, Ewing favored grouping according to histogenetic origin, namely: (a) bronchial epithelium leading to squamous cell carcinoma; (b) bronchial mucous glands leading to adenocarcinoma; and (c) alveolar cell carcinoma (4001). Other pathologists disagreed on the alveolar cell origin and instead favored major grouping into undifferentiated or small cell carcinoma, and differentiated including adenocarcinoma and squamous cell carcinoma (3023, 3029, 3424, 3523). Adenocarcinoma of the human lung had similar histologic appearance as adenomatosis or jaagsiekte in sheep (3938). Contrary to enthusiastic predictions,

during the next forty years, the sheep disease proved to be inapplicable for research on human pulmonary adenocarcinoma.

The search for case reports was conducted as completely as possible to answer the fundamental question: What were the common etiologic factors subscribed to by clinical investigators of lung cancer during the 1930's? Since there were no computerized database, literature search was conducted visually and manually and I am certain that most significant publications were retrieved. Only 5% of 223 articles (4712 patients) contained information on smoking habits, and 15% contained information on occupational history. From these figures, it can be concluded that physicians writing case reports on lung cancer believed that occupational history was more important than tobacco smoking.

The coverage of lung cancer in the collected publications is not limited to etiology of lung cancer. Review articles on symptomatology, differential diagnosis, radiology and bronchoscopy are included. Treatments by radon implantation and surgery were introduced during the 1930's, with initially encouraging results. These case reports on lung cancer for this decade are more detailed than earlier or later ones. The work history are so varied that I could not find any pattern relating to geography, other than miners in areas known for producing coal and metals.

C. TOBACCO USE AND LUNG CANCER

According to Harris, many surgeons, cancer specialists and other physicians reported that lung cancer patients were "almost always heavy smokers." In his State of the Art (Table 2), two were reported in the 1920's, ten in the 1930's, and nine in the 1940's. More than half were by foreign authors, and a third of these were by Germans. My plan is to discuss eight articles dating from 1930 to 1938. The 1939 publications by Ochsner & DeBakey and by Müller are shifted to the next chapter (IV) because supportive articles appeared during the 1940's. When World War II ended, it became apparent that Müller's followers, E. Schairer and E. Schveniger, from Friedrich-Schiller University in Jena, submitted collaborating publications in 1943 (at the time Hitler was over-running Euruope) under the sponsporship of the Scientific Instutitue for Research on the Dangers of Tobacco (4311). The possible relationship of this anti-smoking group to Nazi medicine is discussed in Chapter IV.

According to Harris, the tabulated contents of literature were useful in the following respects:

> "5.4. Beginning in the late 1920s, many surgeons, cancer specialists and other physicians, reporting their clinical experiences with this relatively new cancer, noted that lung cancer patients were almost always heavy cigarette smokers (Table 2).
> 5.5. During the 1930s and early 1940s, the proposition that cigarette smoking caused lung cancer received increasing scientific support (Table 2). Among the several lines of supporting evidence were the following.
> 5.6. The concept of cigarette smoking as a cause of lung cancer was consistent with the previously recognized link between pipe or cigar smoking and oral cancer.

5.7. Further, while pipe and cigar smoking were linked with oral cancer, the widespread inhalation of cigarette smoke, it was reasoned, should be linked mostly to cancer of the lower respiratory tract. Such an hypothesis was supported by observations in cancer patients relating the site of cancer to the type of tobacco used.

5.8. Moreover, the rise in lung cancer in men parallelled the growth in male cigarette use. The relatively low incidence of lung cancer in women accorded with the delayed emergence of widespread cigarette smoking among females.

The above SOA statements was Harris' version of scientific events during the 1930's. Harris omitted mentioning the fact that most monographers on lung cancer omitted any consideration of tobacco hypothesis. Majority of authors of original publications favored other causes of lung cancer, and specifically denied importance to the theory initiated by Germans that tobacco was the cause of lung cancer.

Lung Cancer Monographers.

It was stated in the Introduction to this Chapter, that lung cancer monographers are the preferred authorities over authors that wrote books on cancer in general and who had not done original research in the field of lung cancer. There are about two scores of lung monographers listed above as Monographer (a) to (x); majority did not mention tobacco smoking as an etiologic factor. On the other hand, almost all of them included discussions of occupational/environmental exposure to fossil fuel products and combustion emission, and hostal factors influencing susceptibility to lung cancer. The pertinent quotations relating to tobacco-smoke are discussed in this subtopic, and those relating to other etiologic factors are discussed under Topics D and

E. Contents of lung cancer monographs are distributed under several Topics so that conflicting issues are individually argued in the original written version.

Ewing's monograph was relied upon by Harris as the "sole" authority on lung cancer in general. Ewing allowed half a page on the subject of coal tar and tobacco-smoke, and his statement "the proportion of smokers among patients with lung cancer is very high," was accredited to Roffo. However, the bibliographic source was not mentioned (page 1115 of ref. 4001). This omission implies to me that Ewing hurriedly added Roffo to the page proof of the text, perhaps at the request of interested parties, because Ewing had not conducted research on etiology of lung cancer.

On the other hand, several lung cancer monographs contained detailed reviews of occupational/environmental factors and tobacco smoking as etiologic factors. I decided to quote the important sections so that the reader can recapture the mood of the monographers who were faced with conflicting opinions. Each monographer, after mentioning selected facts, made his own selection of preferred hypothesis. The choice was one, two, or all three of the following: first, personal habits, including diet and tobacco smoking; second, occupational and environmental exposure to fossil fuel, combustion emissions and other industrial carcinogens; third, hostal factors influencing susceptibility or predisposition to lung cancer.

Monographer (c), Simons: Primary Carcinoma of the Lung (3702). This 1937 monograph contained a review of the origin of the hypothesis that cigarette smoking was a suspected cause of lung cancer. Most foreign references that dated back to the 1920's have been collected for translation. A four-

digit number, matching the Bibliographic Number of this Review, has been inserted into original quotations.

"Adler (1201) first noted that male cases exceed female and attributed the difference to irritation caused by tobacco smoking. One of the four patients whose cases were reported by Scott and Forman (1611) was exposed to both heavy tobacco smoke and heavy chemical vapors. Seyfarth (2421) allowed that inhalation of tobacco smoke may have more or less bearing on the origin of lung cancers. Berblinger (2529) admitted that smoking may be an additional causative factor in pulmonary cancers, and Fahr saw an increasing stimulus in the inhalation of cigaret smoke.

In 36 of his cases Hoffman (2911) found no evidence of absorption of nicotine; while among 29, 17 were excessive smokers, seven were cigar makers, one was a cigaret maker and the other smoked, but not to excess. In 17 cases the patients were women, concerning whom it was hard to determine the influence of smoking. Hoffman added Tylecote's information (2719) that in almost every case he saw or knew of the patient was a regular smoker, usually of cigarets; two of the exceptions were women who lived near railway stations where engine smoke continuously pervaded both houses and gardens and who succumbed unusually rapidly to the disease.

Ninety per cent of Arkin and Wagner's patients (3613) were chronic smokers, and these authors believed that inhalation of tobacco smoke may be an important factor in producing chronic irritation with epithelial metaplasia in the bronchi and bronchioles. Oberndorfer (2330) considered smoking and influenza the principle etiologic agents of bronchiogenic carcinoma. Vinson (3215) has merely noted the fact that 70 of 140 cases of carcinoma of the tracheobronchial tree were smokers. Owing to the amount of tar and methyl alcohol contained in tobacco, Ferrari (3331) considered smoking and important etiologic agent of lung cancer. He stated that in Trieste, where more tobacco is used than in any other Italian province, the incidence of pulmonary carcinoma is the greatest. Lickint (2931) cited reports indicating that cancer of organs within the so-called smoke tract - the lips, oral cavity, larynx and bronchi - is more frequent in smokers than in non-smokers. He showed that as the habit of inhaling the smoke increases, the incidence of bronchial tumors increases likewise. However, he conceded that not all bronchial cancers which develop in smokers are caused by tobacco but expressed the opinion that tobacco is the chief cause in a majority of the cases. In many cases the effect of tobacco concurs with other carcinogenic factors. He concluded that it cannot be doubted that tobacco smoke plays a role in etiology of bronchial carcinoma, as a result of which persons whose family history indicates a predisposition to cancer should be advised against smoking.

> The mere fact, stated Staehelin (2526) that there are more men than women smokers and more male than female cases of lung cancer is not sufficient proof of the etiologic influence of smoking. Kikuth (2527), finding little history of smoking among his cases, believed that pulmonary carcinoma would have to occur much more frequently among those who smoke to excess before this could be regarded as a big factor. Katz's view - that in this connection one should keep in mind the Orient, where smoking has been practiced long and extensively - is scarcely pertinent since there are no figures from that source. If increased smoking were responsible for the assumed rise in incidence of pulmonary cancer, then, maintained Passey and Holmes (3537), carcinoma of the tongue, pharynx and larynx should have increased in incidence in proportion to the increase found in carcinoma of the lung.
>
> Tobacco smoke as a lung irritant may be considered among possible causes of pulmonary carcinoma but cannt be counted an important one in the present state of information." (pages 89-91 of ref. 3702)

In the above quotation, Simons questioned the opinion of Katz and simply reiterated the proponents of each side of the controversy. Simons concluded that tobacco smoke "cannot be counted an important one in the present state of information." A similar statement appeared in a 1935 article by Simons, two years prior to the appearance of the monograph:

> "Adler first noted that male cases exceed female, and attributed the difference to irritation caused by smoking. Berblinger (2529) admits that smoking may be an additional causative factor in lung cancers, and Fahr sees an increasing stimulus in the inhalation of cigarette smoke.
>
> The mere fact, says Staehelin (2526), that there are more men than women smokers and more male than female cases of lung-cancer is not sufficient proof of the etiologic influence of smoking. Kikuth, finding little history of smoking among his cases, thinks that lung-carcinoma would have to occur much more frequently among those who smoke to excess before this could be regarded as a big factor.
>
> Tobacco smoke as a lung-irritant may be considered among possible causes of lung-cancers, but cannot be counted an important one in the present state of information." (page 640 of ref. 3525)

Two years after the appearance of the monograph, Simons continued to make the statement that "trauma, general hygiene, roentgen rays, the inhalation of dust,

tar particles, motor exhaust fumes, war gases and tobacco smoke may each be responsible for a very few of these neoplasms, yet proof that any one of them is etiologically significant is lacking" (3824).

Monographer (o), Davidson: Cancer of the Lung and Other Intrathoracic Tumors. The discussion of etiology was highlighted by the following paragraphs:

> "The aetiology of primary lung cancer, which has been the subject of so much speculative investigation in the last few years, is at once the most urgent and the most difficult matter. Apart from the coventional consideration of figures relating to age and sex incidence, questions of heredity, trauma, occupation, and so forth, which naturally form a basis for the aetiological discussion of most cancer problems, the peculiar increase in this special form of the disease - and this we are assuming to be a genuine fact - has led to a vast amount of inquiry, with the result that numerous theories have been advanced, mostly relating to the factor of irritation in some form or another of the respiratory literature on this subject gives the impression at first that considerable number of cases have been investigated, this is perhaps somewhat fallacious. A good many of the statistical observations on this point have been duplicated, to say the least of it, and furthermore it needs but the most elementary knowledge of statistical work to enable us to realize that a far greater bulk of facts must be available before it will be possible to draw conclusions of any real scientific value.
>
> One of the regretable obstacles to the pursuit of truth is the fact that human nature is prone to grasp at straws, and nowhere is this more apparent than in the history of medicine, especially in those branches of it which deal with the causation and treatment of great national scourges such as cancer and tuberculosis. It must therefore be remembered, in discussing the various suggestions that have been put forward to account for the increased incidence of new growths of the lungs and bronchi, that we are dealing with a subject the intrinsic difficulty of which is that of the aetiology of cancer generally, and that in respect of the various conditions producing irritation, no sufficiently large mass of reliable facts has so far been collected to enable us to deduce any real principle of cause and effect. With this preliminary caution, it is of some importance to consider the various points which have been put forward by different observers.

> Tobacco, war gas, petrol fumes, dust, and tar from the roads have all been subject to discussion as possible and likely sources of irritation, but it cannot be said that any observations have been made so far which justify definite conclusions as to the aetiological importance of these factors, and such control evidence as there is does not lend much support to the theories in its favour." (pp 31-34, ref. 3003)

It should be noted that tobacco and other inhalants are covered in one sentence as "possible or likely sources of irritation." Davidson, unlike Simons, subscribed to the primary importance of hostal factors influencing susceptibility.

Monographer (g), Klotz: Primary Carcinoma of the Lung. Klotz regarded each inhalant separately into tobacco smoke, dust from tarred roads, fumes from gasoline engines, and pollution of the air in industrial centers, and dusts in mines. The discussion on tobacco smoke was critical of Hoffman and McNally, highlighted in Harris' SOA report:

> "The alleged increase in the incidence of lung tumors has resulted in an analysis of the habits of modern civilization in the hope of discovering some predisposing factors. Thus, smoking of tobacco, exposure to dust from tarred roads and the inhalation of fumes from gasoline engines have all been incriminated. McNally (3224) suggested that nicotine, phenol bodies, pyridine bases and ammonia, contained in cigarette smoke, were irritants which could account for 'cigarette cough,' chronic bronchitis, leukoplakia and the recorded increase in cancer of the lung. Hoffman (3131), on the basis of elaborate and confusing statistics, concluded that smoking habits unquestionably increase the liability to cancer of the mouth, esophagus, larynx and the lungs. Hoffman adds the astounding statement that non-smokers are subjected to the same dangers owing to air pollution by smokers. However, it is more than likely that smoking is of absolutely no importance. The available statistics are open to far too many objections to bear any weight. Bronchial cancer is common among non-smokers, and indeed Brockbank (3222) found but 14.5% of his cases heavy smokers, while 21% were non-smokers. Furthermore, if smoking were a factor of any importance it is probable that a striking change in sex incidence would have been observed owing to the rapidly growing prevalence of the habit among modern women." (page 450 of ref. 3802)

On the other hand, Klotz was less critical of the role of coal tar and fossil fuel combustion products. There was a third group of monographers who were critical of the role of tobacco smoke but more so of coal tar, fossil fuel products and combustion emissions.

Tobacco Smoking versus Occupation/Environmental Factors.

Publications dealing on clinical observations on lung cancer patients usually incude a brief review of etiology. The scope of etiologic factors generally range from first, critical of tobacco smoking but less critical of occupational/environmental factors; second, critical of tobacco smoking and of occupational/environmental factors but favor hostal factors influencing susceptibility to lung cancer; and third, mention without criticizing tobacco smoking, occupational/environmental factors, and hostal factors. Those belonging to the third group are simply listed, but sample quotations for the first and second group of authors are included below.

Authors critical of causal association of tobacco smoking to lung cancer. Duhig, from Brisbane Hospital for Sick Children, (3220), agreed with an earlier article by Hueper that excluded tobacco smoke as an important cause of lung cancer (2933). Duhig also favored the causal importance of "atmospheric dust and in particular, dust containing known carcinogenic agents, tar from roads and that of a kind smilar to the notorious Schneeberg mine dust" (3220). Fennel, from Honolulu Clinic, stated that "inspite of a tremendous increase in the consumption of cigarettes by both sexes, no one has yet offered a good evidence that it plays a role in the etiology of lung cancer - that is a consolation to many middle aged physicians" (3612). On the other hand, Fennel

expressed the opinion that "at present, the most dangerous irritation factor "is the use of automobiles on tar covered roads."

Donald S. King, from Massachusetts General Hospital, during the discussion of his paper entitled "Primary Cancer of the Lung," was asked to explain the high percentage of cancer of the lung in men and very low percentage in women. King's answer was:

> "I cannot answer that. No one, of course, knows the cause of cancer. Everyone has tried to discover some irritant of the respiratory tract which might be responsible. The use of tobacco is always mentioned as a possibility, but it has never seemed to me to be a satisfactory explanation." (p 833, ref. 3823)

Cecil V. King, from the Gallinger Municipal Hospital, D.C., discussed etiology in an article entitled "Primary Carcinoma of the Lung:"

> "The cause of carcinoma of the lung is similar to that of cancer elsewhere, particularly regarding inherent predisposition, age, race, etc. Irritation may be a factor, notably in certain miners who inhale radioactive dust. Also, pulmonary infections, such as influenza have been said to predispose to cancer of the lung. Tuberculosis is more common at an earlier age than cancer, so that these are not often found together. Recently, however, McNally (3224) has called attention to the fact that cigarette smoking has increased very much in the past 20 years, which increase parallels the rise in cancer; and it is possible that in some cases this source of irritation may be a factor. In the experience at this hospital cancer of the mouth has been seen quite frequently at the site where an old tobacco chewer has repeatedly held his tobacco. Certain it is, also, that cancer of the lung is found in the male about 3 times as frequently as in the female; but this is true also of primary carcinoma of the liver, Hodgkin's disease, and possibly other forms of malignancy." (page 37 of ref. 3413)

Warner, from the University of Maryland, was critical of the hypothesis that inhalation of tobacco smoke was the cause of high incidence in man - "no convincing statistics have been offered to substantiate the assumption that this physical factor has any etiological bearing in bronchogenic carcinoma" (3519).

Authors critical of role of tobacco smoke and occupational/ environmental inhalants. The next group of publications were critical of extrinsic factors in general, and appeared to favor host susceptibility. Sweany, from Chicago Municipal Tuberculosis Sanitarium (3445, 3539), was critical of McNally (3224), who coincidentally was also from Chicago:

> "Recently McNally has pointed out that the increase in lung cancer parallels the consumption of cigarettes. This theory is one that offers one of the best explanations that has been suggested up to the present time, because of the close conformity of the lung cancer curve to the increase in the consumption of cigarettes. Nevertheless, more apparent things than that have failed to prove up, so we must wait and see what experiment will bring. If there is any merit in this theory, it should be manifest in the female sex, where the increase in the use of cigarettes has been greater than in men. If, for example, the ratio of men to women twenty years ago was 3 to 1, and now it is 1.5 to 1, the case is well nigh proved. So far, no such increase in ratios has appeared, for the sex ratio was and still is around three males to one female, similar to other malignant conditions other than those of sex differences. On the other hand, there are many patients with lung cancer who do not give a history of cigarette smoking at all.
>
> As other suspected factors are studied, the probability of their relationship to the cause of lung cancer becomes more remote, and in fact many approach the realms of improbability. Such, for example, are the various chronic diseases that have been accused - certain races, smoke, dust, tar, dusty occupations, and many more, none of which when critically analyzed produce more lung cancers than the others, and all have a proportionate quota not having the disease.
>
> After carefully studying the many possible agents accused of causing lung cancer, it seems that only the radium ores can be definitely indicted. But this is an expected result and certainly is in a different category than most other irritants, because radium emanations brutally alter the germ plasm of any germinative cell." (pages 563-564 of ref. 3444)

If McNally could not convert his own colleagues in Illinois, it was not surprising that New Yorkers ignored him. Hochberg & Lederer, from New York Jewish Hospital, stated in their article on "Early Manifestations of Primary Carcinoma of the Lung":

"Numerous theories have been advanced as to the bearing of inhalation of dusts or of tar from roads as a possible etiologic factor in carcinoma of the lung. No evidence of any such connection has ever been proved. Nor have tuberculosis, influenza, tobacco and war gases been shown to be etiologic agents." (page 81 of ref. 3929)

Passey and Holmes, from the University of Leeds, in their study on the incidence of intrathoracic neoplasia in the teaching hospitals of Great Britain, discussed the contribution of occupational/environmental inhalants:

"It is agreed by most writers that cancer of the lung is more common in the male. This higher incidence in males is claimed by some to be of aetiological importance, and in consequence some writers have attempted to find in our modern mode of life factors which might bring about this difference in sex incidence. The two most recent prominent changes in our mode of living which have been slected in support of their claim are the great increase in smoking and the use of the motor-car. The first as an aetiological factor has received no support from work in the laboratory. If in reality this was the main determining cause of the so-called increase in lung cancer, how can the supporters of this theory explain the fact that cancer of the tongue, larynx and pharynx have not increased in proportion to the increase which they claim to detect in the case of the lung, which, after all, is the last part of the respiratory tract to be exposed to its influence?

The case against the motor-car is supported by two schools, composed of those who think the pollution of the air of our narrow streets by exhaust fumes is the determining factor and those who blame the tarring of the roads. The former hypothesis has nothing whatever to support it. No one has yet shown that garage hands are specially prone to lung cancer. If tarring of the roads is a responsible factor there has never been demonstrated any susceptibility to lung cancer in taxi-drivers, tram, or motor-omnibus drivers and conductors, or in those who drive commercial vehicles or act as chauffeurs. Is there any evidence of a higher incidence in the thousands of men who tend our roads, or in those members of the Police Force of the Automobile Association and the Royal Automobile Club, whose daily occupation is to stand on duty at points of traffic concentration and at cross roads where it is reasonable to expect that suspension of road dust in the air would be at its maximum?

Tarring of the roads did not become general in this country until the War period, whereas the rise in the lung-cancer incidence, which some profess to see in Duguid's table, shows itself as early as 1901-5 and is firmly established by 1911-15. The accompanying Table VII given by Bridge and Henry in a communication dealing with industrial cancers shows that workers in the indust-

> ries closely connected with tar and other allied carcinogenic compounds require an exposure under fairly intimate circumstances for very long periods before cancer, mostly of the cutaneous surfaces, first appears.
>
> It is reasonable to expect that lung cancer, if induced by inhalation of tar-contaminated road dust, would require at least as long a latent period before making its appearances. Campbell (3453) has recently shown that the exposure of mice to an atmosphere highly contaminated with a sample of road dust, containing 2 per cent. of tar, is capable of inducing malignant tumours of the skin. It is significant, however, that up to the time of the publication of his article he had completely failed to induce primary lung cancer, although the experiments had been in progress for more than a year, whereas the first skin tumour appeared in six months. By analogy it seems reasonable to expect that the inhalation of tarry dust would take longer in producing tumours of the lung in men than such frequent application of tar to the skin as occurs in the tar and allied industries referred to in the Table. Thus, if indeed there be anything in this hypothesis, it is certainly not reasonable to expect lung tumours in man, in any numbers, for some years yet to come. In short, tarring of the road has not been in progress for a sufficient length of time to produce the changes in the incidence of lung cancer which many claim they can detect by their statistical methods, especially those who find this increase commencing in the pre-war or early post-war years." (pages 334-335 of ref. 3537)

Passey and Holmes were critical of tobacco smoke and tar particulates probably because they could not find any increase in lung cancer incidence. It should be noted that Passey and Holmes treated the two as separate causative factors, i.e., personal exposure versus occupational/environmental exposure.

Authors who mention tobacco, coal tar and host susceptibility. More than 400 articles on clinical aspects of lung cancer were examined for the preparation of this chapter. Most of them (90 percent) did not mention tobacco smoke as a causative factor. The following articles, mostly case reports, mention tobacco, coal tar and host susceptibility in the list of causative factors. The authors did not comment whether they believe in the tobacco causation. It is interesting that smoking habits of the lung cancer

patients were not included in case reports, even though the introduction alluded to the theory of tobacco smoking as a causative factor. The relevant articles derived from the 400 lung cancer articles are as follows:

Bib. No.	Authors	Geographic Location
(3011)	Bonner	Georgia
(3715)	Pierce & Ingersoll	Michigan
(3729)	Donald	Michigan
(3113)	Allen & Smith	Michigan
(3030)	Goltz	Michigan
(3223)	Tyler	Nebraska
(3526)	Neely	Nebraska
(3930)	Howes	New York
(3119)	Menne, Bisaillon & Robertson	Oregon
(3831)	Warmolts	Pennsylvania
(3532)	Smith	South Carolina
(3416)	Jermain	Wisconsin
(3446)	Ellis	Manchester (Great Britain)

The above table concludes the survey of publications in response to the question: What was the prevalent opinion on the cause of cancer? About 90% of lung cancer authors did not believe tobacco smoking was an etiologic factor to be investigated or even mentioned in monographs, review articles or clinical publications. Under Topic D, the acceptance of occupational/environmental exposure as important etiologic factor is reviewed for the same decade.

Prevalence of Cigarette Smoking in Lung Cancer Patients.

Harris' Table 2 included articles that supported the "preposition that cigarette smoking caused cancer." There were nine articles dating from 1927 to 1936; the 1937 article by Ahlbom related largely to oral cancer; and the 1939

articles by Ochsner & DeBakey and by Müller are reviewed in Chapter IV because critical reservations were expressed during the 1940's.

I composed the following table of scientific articles dated from 1903 to 1938 on the prevalence of cigarette smoking in lung cancer patients. Nine were copied from Harris' Table, whereas 22 entries were from my own manual search of the literature.

(Bib. Number) Author, Geographic Location	Entry in Harris' SOA Table 2 Case Material/Clinical Observation
(0943) Musser (PA)	Clerk, smoked moderately, drunk tea and coffee
(0945) Packard (NY)	Cigar maker
(1611) Scott & Forman (?)	Four gave history of excessive tobacco smoking
(1711) Packard (NY)	Cigarmaker
(1811) Packard (NY)	Cigarmaker
(2117) Friedman (NY)	Smoker, had scarlet fever
(2215) Dana & McIntosh (NY)	German cook; also cigarette smoker
(2319) Folsom (D.C.)	Cigarette smoker; merchant, had typhoid fever
(2421) Seyfarth (Germany ?)*	Quoted Brinkman & Engel's report of lung cancer in cigar smokers
(2615) Perry (DC)	Cigarette smker, had adult whooping cough
(2622) Bel (LA)	Cigarette smoker, contracter
(2711) Perret (LA)*	Harris: "Review of 6 cases of cancer within chest cavity. All 4 of the lung cancer cases for which smoking histories were available reported 'excess use of tobacco'. Although fully realizing that our series of cases is too small to draw any general conclusions, we have been struck by the excessive smoking of many of the patients, and that all the cases occured in males."
(2719) Tylecote (GBR)*	Harris quoting Tylecote: 'I have no statistics with regard to tobacco but I think that in almost every case I have seen and known of the patient has been a regular smoker, generally of cigarette.' (see also DMA page 84)
(2925) Hunt (CAN)	Cigarette smokers: 20 M and 6 F (?)
(2931) Lickint (GER)*	Harris: "Review of laboratory and clinical evidence on tobacco and cancer. Rise in cigarette use linked to rise in lung cancer."
(3031) Mertens (GER)*	Harris: "Increased incidence of lung cancer linked to tobacco. Shift in cancer from oral sites to lower respiratory tract linked to shift from pipes and cigars to inhaled cigarettes."
(3131) Hoffman (MA)*	Harris: "Analysis of San Francisco Cancer Survey. Review of nation-wide vital statistics. 'I

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	am strongly inclined to think that the increase [in lung cancer] is directly connected with the much wider spread of cigarette smoking habits, including the inhaling of smoke which must enter the lungs to a considerable extent in many cases.' 'The observed increase in cancer of the lungs during recent years is highly suggestive of its correlation to the immense spread of cigarette smoking habits.' 'Yet smoking habits have proportionately increased faster among women during recent years than among men. But the fact must not be lost sight of that the injurious effects of tobacco smoking in their relation to cancer probably require quite a long period of time to become noticable.' 'The increase of cancer of the lung observed in this and many other countries is in all probability to a certain extent directly traceable to the common practice of cigarette smoking and inhalation of cigarette smoke. The latter practice unquestionable increase the danger of cancer development.'
(3212) Rogers (CA)	"Irritating fumes of any sort, with the possible exception of tobacco, did not seem to play a role; 72 percent of this group (50) were smokers."
(3215) Vinson (MN)	Less than half of patients (32) were smokers; only a few smoked to excess.
(3222) Brockbank (GBR)*	"In my series nine (15 per cent) smoked excessively, six smoked thick twist, whilst thirteen (21 per cent) never smoked at all."
(3224) McNally (IL)*	Harris: "Review of chemical constituents of cigarette smoke and their biological effects. 'Comparing the enormous consumption of cigarettes in 1925-1931 with the increase in pulmonary cancer, one is certainly led to believe that cigarette smoking is an important factor in the increase of cancer of the lungs.' 'The tar of cigarette smoke contains nicotine, phenolic bodies, pyridine bases, and ammonia, irritants which could account for cigarette cough, the chronic bronchitis of the cigarette smoker, the leukoplakia in heavy smokers, and the recorded increase of cancer of the lung.'
(3327) Pilcher & Brindley (TX)	"In our series it is interesting to note that five of the eight men patients were heavy smokers of cigarettes, although this may not be greater than any selected group of men."
(3540) Thys (BEL)*	Harris: "Review of etiology of cancer. Observed shift in cancer incidence from oral cavity to lung explained by the change from noninhaled pipes and cigars to inhaled cigarettes. 'En conclusion, il

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	noussemble legitime de faire un rapproachement entre le cancer bronchique, cancer des fumeurs d'apres-guerre, et al vogue de la cigarette. Cette notion complete simplement celle des classiques qui imputent a la pipe le cancer labial et lingual, vieille forme du cancer des fumeurs.'
(3603) Craven (NY)	"Claim have been made, both for and against the etiological role of tobacco smoking in cancer of the lung. In 48 male patients with cancer of the lung who gave a statement about their use of tobacco, 31 or 64 per cent were classed as having smoked to excess. In 10 instances this history of heavy smoking was associated with the factor of an occupation that was probably irritation, in 3 instances with a history of repeated or severe respiratory infections, and in 4 instances with both an occupational factor and a history of respiratory infections. On the whole, these figures do not seem very impressive, and seem almost to call for the assumption of some additional factor of special susceptibility of the bronchi to forms of irritation that are probably present to an almost equal degree in subjects who do not develop cancer of the lung."
(3613) Arkin & Wagner (IL)*	Harris: "135 cases of lung cancer diangosed over 4-year period. 'Ninety percent of all our patients were chronic smokers, and we believe that the inhalation of tobacco smoke may be an important factor in producing chronic irritation with epithelial metaplasia in the bronchi or bronchioles.'
(3627) Fleckseder (AUS)*	Harris: "Among 54 male cases of bronchial carcinoma, 94.4% smoked and 68.5% were heavy cigarette (as opposed to pipe and cigar) smokers. 'So erklart sich wohl der Umstand, dass unter unseren Bronchialkrebskranken die starken Zigaretten raucher in der Ueberzahl waren, sie bringen eben durch das sogenannte Inhalieren den Tabakrauch in ausreichender Konzentration in die grosse Luftwege, wahrend Zigarren- und Pfeifenraucher den Tabakrauch zumeist nicht so tief einzeihen.'
(3720) Frissell & Knox (NY)	"In our series of cases occupation did not play a significant part. There were no miners in the series and only 3 were engaged in dusty trades - a bricklayer, baker, and fireman. Neither were the habits of the patients of significance, except for the well-nigh universal use of tobacco. One had been a victim of war gas. Ten of the cases were in females, 36 in males."

(3724) Husted & Bulman (DEN)	"With regard to the significance of the noxious influence of some particular occupations, the present material offers absolutely no suggestion of that kind. These patients, eight women and 27 men, came from all classes of society and represented a quite accidental mixture of all occupations, without predominant frequency of any occupation or group of workers. It is quite true that no mining is done in this country, but apart from one patient who was a stoker the material contains no cases of which it would be reasonable to assume that the patient had been exposed to the effect of dust and smoke more than all other persons in general. In this connection it is also to be mentioned that any marked degree of anthracosis of the lungs was found on two cases only. Tobacco has frequently been discussed as an etiological factor, but our patient material includes no tobacco workers, and according to the case records only four of the patients were particularly heavy smokers." (pages 152-153)
(3830) Bauer (PA)	"One patient (Case 21) the clinical record stated definitely that tobacco was not used. In fifteen the use of tobacco ranged from a few cigarettes to several packs or several cigars or the increased use of a pipe daily" (page 282). No other information was mentioned in records of 16 other cases of primary carcinoma of the lung.
(3833) Faget & Harmos (VA)	"All of our patients were heavy smokers." A total of six patients. (pages 22-23)
(3825) McGavack (NY)	"Fourteen of the 90 instances of pulmonary carcinoma here discussed were heavy smokers, using either a package or more of cigarettes, or four or more cigars daily. In all, 60 patients used tobacco to a greater or lesser extent. Summarization of the literature leaves one with the impression that the influence of tobacco in causing or predisposing to pulmonary cancer is highly problamatical." (page 132)

* Also referenced in Larsen's Tobacco Monograph (6101).
Note: The two-letter geographic abbreviation signify postal abbreviations of the United States; the three-letter are for foreign countries.

The above list is more comprehensive than the tobacco monograph by Larson, Silvette & Haag (6101). Only eight out of 31 entries are included in the tobacco bibliography. The eight publications selected by Harris are grouped

further into nationality of authors from: Germany, Great Britain, Belgium, Austria and the United States.

German articles. The first suggestion that tobacco smoking caused lung cancer was attributed by Seyfarth (2421) to Brinkman & Engel. Lickint, from the Municipal Hospital of Kuchwald, Chemnitz, did not offer any original observations on patients but simply listed the following authors who "attribute at least partial blame to tobacco, particularly, cigarette smoking (2931):"

Berblinger: Klin Wschr 913, 1925.
Fahr: Verh pathol Ges Gottingen, 1923.
Ferenczy & Matolczy: Wien klin Wschr No. 19, 1827.
Hochstaetter: Klin Wschr 1092, 1926.
Kanngiesser: Bl f biol Med Hamburg, 1936.
Schönherr: Z Krebsforschg 27: 436, 1928.

I have not seen the above articles and an English translation will be needed to find out the number of patients and prevalence of smoking. Lickint indicated in his review that "for the increase incidence of lung cancer, a number of causes have been considered: better diagnosis, frequent occurrence of influenza, automobile combustion gas, street dust, road tar, combat gas and other." (page 10 of English translation of ref. 2931)

The 1930 publication of Mertens from the University Hospital at Munich, was a review of literature on increasing incidence of lung cancer. I cannot find the source of Harris' statement from the English translation (3031). The article was largely a description of experiments exposing mice to cigarette smoke, and are discussed under the next subtopic, together with German experiments on skin painting. It should be noted that prior to 1939, there were no specific figures on prevalence of smoking among German lung cancer patients and among the general population.

British studies. The 1927 letter to the Editor by Tylecote (2719) has been discussed in Chapter II, pages 84 and 101. Brockbank's report that included smoking habit was intended to determine occupational incidence of primary lung cancer. In 62 cases investigated in some detail, nine (14.5 percent) seemed to have definitely dusty jobs, and eighteen (29 percent) worked among gases and fumes. Four were badly gassed during the war and nine smoked excessively. Brockbank concluded that "poison war gas, tobacco smoking, road dust and motor-car fumes are all possible aetiological factors." (page 37 of ref. 3222). He did not make any statement implying that there was a common denominator for all inhalants and that results of experimental studies were interchangeable.

Belgian studies. Thys, from the Foundation Medicale Reine Elisabeth in Brussels, wrote an article on the etiology of bronchial carcinoma (3540). In an effort to explain the increased incidence of lung cancer during the past two years (24 males, 1 female), Thys reviewed the literature starting with lung cancer in miners, and concluded with tobacco smoke. The reasoning Thys used appears to me to be similar to that used by his German colleagues during the 1930's and more recently, by Harris:

> "If we have just now insisted on the fact that iron, coal and slica mine workers are not particularly exposed to pulmonary cancer, we should nevertheless, remember that Sekoulitch, already in 1925, pointed out the frequency of cancer of the larynx in those who worked with wood. There again, is it a physical of chemical action with which we are dealing? Are the tannins and wood oils carcinogenic to the same extent as tar? Because tar, one of the most clearly carcinogenic agents that we know of, has of course also been used to explain the progressive increase in cases of pulmonary cancer. The theory which ties bronchial carcinoma to the action of dusts impregnated with tar which we can inhale daily on a more frequent basis is certainly interesting. We need only remember that from 1922 to 1929, the quantity of asphalt on the roads of France has increased from one to ten.

Accordingly, we can see in the use of tar on these roads a carcinogenic cause of the first order which constantly grows in importance. But if bronchial cancer is caused by the inhalation of tar dust resulting from the asphalting of our roads, how can we explain its almost complete absence in women? It is therefore not there that we will find the explanation we are seeking.

But if it is effectively true that one must realistically incriminate the vapors of tar, at this point, we see, somewhere other than on the roads, a 'tarring' factor.

It is astonishing that publications dealing with pulmonary cancer have not yet mentioned tobacco smokers. In effect, when consuming tobacco, what are we ingesting if not a dry distillation of the cellulose which provides relatively strong quantities of tar.

We have long known about the irritative action which tobacco smoke has on the buccal mucous membrane. We spoke readily, a few years ago, of smokers cancer to designate the epithelium of the lips. But how do we explain that, having localized itself up to now in the buccal epithelium, this cancer now shows a marked tendency to displace itself toward the lower respiratory tract?

The explanation behind this sort of migration is simple when one thinks, as Professor Nolf has pointed out to us, about the difference in habits between yesterday's and today's smokers. In effect, just a few years ago, tobacco in our country was consumed mainly in a pipe; less in a cigar; cigarettes were rarely seen. At the same time, we reiterate, we were content to note a link between labial cancer (and lingual) and the irritation in the lips and tongue caused by the mouthpiece of the pipe and the tobacco smoke directly hitting the periphery of the mouth. The phrase 'Smoker's Cancer' was quickly coined.

Nowadays, in contrast, tobacco is mainly consumed in the form of cigarettes; the pipe has been abandoned and the average man today prefers a pinch of tobacco rolled in paper. The post-war period was the unprecedented fashion of the cigarette adopted by the masses. And it is precisely in this consumption of cigarettes, carried to excess, in which can perhaps be found the basic cause of pulmonary carcinoma. Because, in effect, with both the pipe and the cigar, the smoker is only 'tarring' his mouth (no inhalation); with the cigarette he is 'tarring' his bronchial tubes (total inhalation). This is because tobacco from a pipe or cigar gives off an acrid smoke which cannot be passed on into the lower respiratory tract without provoking a coughing fit. In contrast, cigarette smoke is not very irritating, often perfumed, and most smokers inhale it. This smoke undoubtedly penetrates very far, definitely entering into contact with the bronchial mucous membrane. This tar inhalation is even more dangerous for the bronchial epithelium as the very hot cigarette vapors are cooled far less than those of the cigar (which is longer and only two thirds consumed) or the pipe, in which the stem cools the smoke passing through and collects the tar which has been

liquefied. In a word, this high temperture maintains the volatile state of the tars which would otherwise (in a cigar or pipe) be condensed and deposited prior to penetrating the organism.

If one therefore wants to admit the carcinogenic action of tobacco consumed frequently for a long time, it is ready for us to understand why, in one case, the neoplasia affects the lips or the tongue, in another, it is found in the bronchial tubes. With cigarettes and the deep inhalation of its smoke, one would almost be able to speak of tar applications on the bronchial mucous membranes, like the skin applications that we performed on mice in our cancer laboratories. We thus suspect the cause and frequency of cancer in men (95%), its rarity in women (5% from our statistics) who very rarely smoke or inhale the smoke. It was easy for us to state that in most cases, pulmonary cancers that we have examined, exist in heavy smokers and especially cigarette smokers.

Some will perhaps object by pointing out that there have been heavy cigarette smokers throughout history and that no one has noted in them the frequency of pulmonary cancer. But until these last few years, such smokers belonged to the leisure classes. So what is there to tell us that many of these smokers did not end their days because of undiagnosed cases of pulmonary cancer? For the attention of the doctor has only recently been drawn to bronchial carcinoma and it is probable that many of the cases involving private practice were not, and are still not, properly diagnosed as such (this diagnosis can only be made through the use of radiography or at the autopsy table).

In accordance with Professor Nolf, we again underline this point while recalling that the statistics of high frequency of pulmonary cancer are hospital statistics relating almost exclusively to cases among the working class. And, in this class, cigarettes have been in vogue only as of about the last twenty years; also, working class women do not smoke, or very little, which would explain why they are almost completely unaffected by this type of cancer.

In conclusion, it appears to us that a legitimate case can be made linking bronchial cancer, smoker's cancer of the post-war period, and the coming into fashion of the cigarette. This notion simply compliments the classic ones which attribute labial and lingual cancer to the pipe, an old form of smoker's cancer.

There would consequently be a new noxious action to be attributed to tobacco which would undoubtedly be useful to study more closely. In the fight against tobacco use, it seems to us that we are too often led to consider only the action of nicotine.

Notably Lickint (2931), in proposing regulations which have as their aim establishing restrictions on smokers, appears preoccupied only with the nicotine action of tobacco. And if it is true, as he believes, that it is time to call upon the press (through news conferences, etc.) to methodically educate the public on the dangers of tobacco use, it is perhaps also useful to mention to the public the potential role which the inhalation of tobacco

smoke plays in the cause of lung cancer." (pages 2-4, English translation of ref. 3540)

Thys published another article in 1939 that needs translation (3939). It should be noted that there was a link of communication between Thys and Lickint in 1935 and it would be interesting to question if exchange of ideas continued after Belgium was occupied by the Nazis. I have not examined publications by Holf and Sekowlitch mentioned by Thys.

Austrian studies. Fleckseder, from Rudolfstiftung Hospital in Vienna, examined the records of 62 bronchial carcinoma patients admitted over the past 13 years (3627).

"Finally, I would like to focus on the influence of tobacco smoking on the development of BrCa (bronchial carcioma). 94.4% of the male patients admitted to smoking tobacco; 68.5% of them were heavy smokers. As already mentioned, the strong predominance of men over women in patients with bronchial cancer can most likely be explained by the abuse of tobacco so common in the large majority of our men (Lickint 2931). What could constitute the carcinogenic effect of tobacco smoking? Do we have to deal with an inhalation disorder which affects the bronchial membrane which has already been damaged by the breaking apart and transformation of cells or which, by means of precancerous transformation, causes the development of cancer in an initially normal mucous membrane. Or is it another case of vascular damage which prompts the growth of cancer by means of atheromatous changes on the small arteries of an already altered tissue area? In my opinion, a combined effect of both forms of disorder is most likely. The (part of sentence illegible to the translator) support a direct irritating effect of tobacco smoke on the mucous membrane. In this context, I would also like to note the tendency of smoker leukoplasia of the mucous membrane of the lips and the mouth to develop cancer. In the first case, mechanical irritants of the mouthpiece of a pipe, in the latter case an occasional luetic infection could play a role in the development of cancer (Scherber). The pronounced predominance of cancer of the throat in men can be interpreted in a similar manner as the predominance of BrCa in men. I would like to mention the observations of Brinkmann and of Enger, quoted in Seyfarth (2421), who observed the occurrence of bronchial cancer in cigar producers or cigar workers seven times. We have to assume that tobacco and its combustion products would have to affect the mucous membranes in a continuous manner and in a certain concentration in order to play a carcinogenic role. This explains

the predominance of heavy cigarette smokers among our patients with bronchial cancer, since they inhale tobacco smoke in sufficient concentration into the main respiratory tract, while cigar and pipe smokers usually do not inhale tobacco as deeply. On the other hand, the fact that tobacco abuse promotes the development of arterio-sclerotic vascular changes is well known in hospitals and is fully confirmed by the observations which I have carried out to that regard for many years.

According to our observations of 62 cases of bronchial cancer, the following conditions are of principal importance for the development of a BrCa:

1. Damage in the area of the lungs and the primary bronchial tubes, which occurred prior to the development of the BrCa and which can cause the formation of scars, the separation and dispersion of cells, and possibly the alteration of the epithelium. Such previous damage was demonstrated in 100% of the cases. In our opinion, the most frequent cause in this regard is tuberculosis of the lungs and its lymphatic glands.

2. Vasoconstriction of the arteries which leads to oxygen deficiency in these damaged areas and which probably occurs in conjunction with arterial and age atheromatous hyperitonia and maybe also with lues and chronic lead exposure.

3. In women, a endocrine factor manifesting itself in a gonadal, functional disorder during climacteric and menopause. This condition is found in 100% of the relatively small number of our female patients with BrCa. This simultaneous influence of the vascular factor also needs to be considered here.

4. In the predominant majority of our male patients, abusive tobacco smoking, especially the smoking of cigarettes, which can be an epithelial irritant on the one hand and also cause vascular damage on the other hand." (pages 6-7, English translation of ref. 3627).

Statement 3 may have been extended as a proposed explanation for higher incidence of lung cancer in males than in females. There were animal studies that female sex hormones influenced carcinogenesis. However, this possibility was not seriously considered during the 1930's.

American clinical studies. There were three articles by American clinicians cited by Harris. My first question is as follows: What were the secondary references that might have influenced American clinicians to investigate the role of tobacco smoking? There were actually no reference to

any German or European articles. It was possible that the Americans read foreign articles without alluding to sources.

Harris used the articles by Arkin and Wagner entitled "Primary Carcinoma of the Lung: A Diagnostic Study of 135 cases" (3613). This article was used not only as SOA ref. 6, Deposition Exhibit P6, but also Trial Proceedings Exhibit 51 (pages 822-823, 843-851; I do not have a copy of the cross-examination pages 5967-5969). The key sentence used by Harris was as follows: "ninety per cent of all our patients were chronic smokers and we believe that the inhalation of tobacco smoke may be an important factor in producing chronic irritation with epithelial metaplasia in the bronchi or bronchioles." There was no mention of other etiologic factors.

Two years later, Arkin contributed a follow-up report on a larger group consisting of 160 cases of lung cancer. The article (not used by Harris), included a discussion, not only of tobacco smoke but also of etiologic factors:

> "Among the one hundred and sixty cases, one hundred and twenty, or seventy-five per cent have occurred between the ages of forty-one and sixty years. Fifteen patients or about nine per cent were twenty-one to forty years old. The disease is much more frequent in men than in women. There were one hundred and forty-five men, and fifteen women. Perhaps the inhalation of tobacco smoke is an important factor in causing chronic irritation with epithelial metaplasia in the bronchi or bronchioles. If this be true then the incidence in women should increase, now that women are smoking almost as much as men.
>
> We do not know the cause of malignancy in any tissue or organ at the present time. Chronic irritation, chemical, physical, or mechanical, may cause cellular damage followed by increased rate of growth. Hereditary predisposition plays a role in lower animals (Maude Slye), perhaps also in man. The human lung is exposed to numerous irritants, chemical bacterial and mechanical, any one or combination of which may cause the basal epithelial cells of the bronchi to undergo a metaplasia. These basal cells may produce three histologic types of cancer, (1) undifferentiated round or spindle cell, (2) adenocarcinoma, or (3) squamous cell." (page 370 of ref. 3846)

In an earlier article, Arkin discussed the etiology of lung cancer as follows:

> "As in other forms of carcinoma, we do not know the exciting agent of bronchial cancer. Chronic irritation from smoke, dust, or chemical agents probably is the most important predisposing cause. To this must be added chronic suppurations as in bronchiectases or cavities, tuberculosis, syphilis, foreign bodies, and possibly influenza.
>
> Street dust, coal dust, stone dust, tobacco smoke, and especially exhaust fumes from gasoline and oil of automobiles have been blamed. We know the cancer-producing properties of certain coal-tar products, and perhaps it is these which cause chronic inflammatory changes with metaplasia of epithelium and cancer formation. The writer has seen 8 of 40 cases observed in the past seven years, in foundry workers who handled acid fumes, garage employees, stone-cutters, and people employed in dusty occupations. The increased use of gasolines, oils, and tar products may be an important factor in causing the increase in bronchial cancer in the last two decades. Fibroid processes in the lungs (tuberculous and non-tuberculous) with the formation of bronchiectatic cavities produce a chronic bronchitis, lead to the accumulation of purulent secretions and foreign particles. Epithelial thickenings, metaplasia, and leukoplakia form precancerous lesions. Perhaps here as in other organs a hereditary predisposition is a factor." (page 1256 of ref. 3032)

It should be noted that contrary to Harris' impression, Arkin did not subscribe solely to tobacco smoking as a cause.

Several colleagues of Arkin in Chicago did not mention tobacco smoking in their publications on lung carcinoma: Stein & Joslin (3815) from Veterans Hospital at Hines, Illinois and others listed in the Table of Case Reports (3817, 3818). The following clinicians used Arkin & Waagner as a secondary citation: Volini & Shapiro of Cook County Hospital (3816), McGavack from New York City (3825), and Faget & Harmos (3833) from the U.S., Marine Hospital at Norfolk, Virginia. However, Faget & Harmos referred to the tobacco literature "in causing or predisposing to pulmonary cancer is highly problematical."

Editorials on lung cancer. The Lancet published two editorials on the subject of cancer of the lung. Boycott commented on increased incidence as follows:

> "In the second place, we have had an interesting problem in aetiology to solve and we still have it. Numerical analysis of the more complete data (such as J.B. Duguid (2721), did for the records of the Manchester Royal Infirmary) seems to show that the recent increase began long before pathologists took notice of it - somewhere about 1890 or 1900. If that is so, the influenza of 1918-19 and war gases can have had nothing to do with it. Presumably, therefore, the increase has been caused by some change in habits or mode of life or environment. In speculating what this might be, we cannot put aside the very definite evidence, clinical as well as experimental, that an irritant must act for at least about a quarter of the natural span of life before it produces a tumour; the latent period for mule-spinners' cancer is at the least 15 and on the average 35 years of exposure to the effective mineral lubricating oils. These data, it is true, apply to epitheliomas of skin and may not be directly transferable to tumours of mucous membranes. But something of the same kind must surely be true for these also, and in looking for the cause of bronchial cancer we should probably consider what happened towards the end of last century. The environment as a whole has become less carcinogenic; there is more soap and hot water, less irritating food, the air is cleaner, the general standard of life has greatly improved. We have, on the other hand, much more tobacco and more recently petrol engines and tarred roads; whatever the agent, it produces lung cancer much more frequently in men than in women." (page 959 of ref. 3225)

The above editiorial combined as "irritants", tobacco, petrol, engine emissions and tarred roads in the environment. The second Editorial also appearing in Lancet continued:

> "From centres in nearly all the populous districts in the northern hemisphere we now have reports of a progressive increase in the incidence of cancer of the lung. To the April issue of the Wiener Archiv für innere Medizin Dr. Dinko Sucic contributes a paper on its occurrence in Zagreb in Yugoslavia. His material comprised in all 51 cases, 30 of which were investigated in the pathological institute of Zagreb University during the last ten years. In that institute lung cancers have increased from an average of less than 6 per cent. of all cancers in 1923-25 to more than 18 per cent. in 1929. Such an increase is no unusual finding, but this record is important in view of the fact that

Yugoslavia is an agricultural State with (as Sucic points out) 80 per cent. of its population engaged in farming and the like. This goes to show that the increase in pulmonary tumours is not confined to the populations of the air-polluted industrial centres of the world.

The fact of its increasing incidence makes cancer of the lung particularly interesting to pathologist at the present time, for one may reasonably assume that as the disease is on the increase so must the factors which are responsible for it be on the increase, and hence be the more readily identifiable. On this assumption a number of extraneous agents, associated with the modern increase of industrialism, have been cited as possible causes. These include road dusts, especially from tarred roads, exhaust gases from motor-cars, and factory smoke - all acting through the medium of air pollution. Yet the now well-established fact that these cancers are on the increase in agricultural lands as well as in industrial towns makes it difficult to associate them directly with industrialism, especially as these industries in the various countries concerned are so diverse. Sucic is driven to the conclusion that diverse factors must be concerned indirectly in the carcinogenesis, all of them acting as irritants to the bronchial mucous membrane or alveolar epithelium so as to predispose to cancer development. It is difficult to believe, however, that even a variety of factors could operate with such uniform effect in such diverse places, both urban and rural, as has been the case with the increase in cancer of the lung. One can believe that the atmosphere of large cities may have deteriorated in the last few decades, but not that the atmosphere in the countrysides can have altered correspondingly, and the simple fact that the cancer increase is so general and uniform seems largely to absolve industrial air pollution from blame. A factor which is of much more uniform distribution than industrialism and which merits careful consideration is tobacco-smoking. Already several authorities have suggested this - and especially cigarette-smoking - as a likely cause of lung cancer, and the notion is certainly gaining ground; yet there remains an evident reluctance on the part of many investigators to associate themselves with it. Hoffman (3131) has discussed the question fairly fully, and amongst other notable facts he has pointed out that the consumption of light cigarettes has increased from 53,000 million to 108,000 million between the years 1918 and 1928. There is no doubt that men still remain greater tobacco-consumers than women, and the fact that practically all observers find cancer of the lung to be preeminently a disease of men, suports the suggestion of a direct relationship between it and smoking. Sucic noted that 25 of his 30 cases were in men, and many other observers have found the proportion in favour of men to be even greater than this. If air pollution of any kind is to be seriously considered, therefore, this particular form of it must not escape attention for, no matter whether he be in the fields of Yugoslavia, on the

> mountains of Innsbruck, or in the streets of Manchester, the cigarette-smoker who inhales habitually subjects himself to the most concentrated form of air pollution possible to endure.
>
> Unfortunately, information about the personal habits of past cases is difficult to obtain, so that the data which might yield direct evidence on this point are wanting, and the answer must await the collection of further clinical observations. Several workers have of late tried to produce experimental proof that tobacco is carcinogenic - using such methods as subjecting animals to an atmosphere laden with cigarette smoke, or applying to their skins tar obtained from tobacco combustion. A feature of many of these experiments seems to have been the development of cancer in not more than one animal out of large numbers used in each instance. Such was the case with two independent workers in Germany and the Argentine and also with a group of workers in Birmingham whose results have lately appeared. These negative results are, of course, from the nature of things biological, just such as are to be expected in early attempts at a new line of experimental cancer production, and it would be wrong to conclude from them that tobacco is unimportant as a factor in the causation of cancer. However difficult it may be to prove the case against cigarette-smoking, it has not yet been cleared from suspicion." (pages 1206-1207 of ref. 3226)

Until 1932, results of animal experiments did not support "tobacco tar" as a cause of cancer but were positive for coal tar. The discussion on tobacco use in agricultural areas was not documented by consumption figures. The third Editorial appeared in JAMA a year after the appearance of an article by Arkin and Wagner (3613):

> "Among the contributing factors to this increase, the injurious effects of tobacco smoking, exhaust gases from automobiles, tar on roads and the influenza epidemic of 1918-1919 have been suggested. None of these can be accepted as definitely causative. Arkin and Wagner (3613) state that 90 per cent of their patients were chronic smokers. They believe that inhalation of tobacco smoke may be an important factor in producing chronic irritation with epithelial metaplasia in the bronchi or broncioles. The disease is preponderantly more common in males than in females, about two thirds of all cases occurring between the ages of 40 and 60. Occupation probably does not play an important part and evidence regarding the influence of preexisting pulmonary disease is not convincing. Edwards emphasizes the fact that in a number of his patients the history was peculiarly free from illness in any form. A persistent cough, hemoptysis and thoracic pain of a severe and continous type, in a man past the age of 40, are highly suggestive of pulmonary cancer. However, many of the cases of pulmonary carcinoma may be without pulmonary symptoms, their

earliest manifestations being those of the metastases away from the thoracic cage. Thus, in Arkin and Wagner's series of 135 cases, 51 percent presented extrapulmonary signs and symptoms and only 49 per cent presented symptoms referable to the pulmonary tissue.

Recent histologic studies of malignant lesions of the lung have demonstrated that most of the round cell, 'oat' cell and spindle cell sarcomas of the lung are in reality carcinomas of bronchogenic origin. The majority of the carcinomas of the lung are of the squamous cell type. Tuttle and Womack (2424) call attention to the facility of the bronchial epithelium to change its morphologic characteristics when subjected to trauma or chronic irritation. The hyperplastic and metaplastic changes taking place may in reality be the first step in carcinogenesis. Attractive as this theory seems, it has found little support in clinical facts. Tuttle and Womack themselves state that of the seventy-six cases of primary bronchiectasis in persons of the cancer age seen in the chest service of the Barnes Hospital there has been observed only one patient who subsequently developed bronchogenic carcinoma. Bronchopulmonary carcinoma displays a tendency to give rise to metastases to the liver, bones, spleen, pancreas and, with a characteristic freequency, to the suprarenals and the brain. According to Tuttle and Womack, tumors of the major bronchi give symptoms early, extend more slowly and are more amenable to surgical treatment, while tumors of the minor bronchi and of the periphery of the lung cause fewer early symptoms and are more rapidly fatal." (page 1716 of ref. 3730)

Smoking habits of population groups. Hoffman interviewed non-cancer patients in San Francisco, suffering mostly from chronic diseases of adult life, chiefly, heart disease, arteriosclerosis, arthritis, hypertension, diabetes, nephritis and other diseases. From responses of 537 male patients, 42.3 percent reported themselves as "heavy smokers" which is comparable to 45.6 percent for cancer patients. Hoffman concluded that "the differences are therefore very slight, which may be construed as opposed to the theory that smoking habits increase materially the liability to malignant tumors." Hoffman commented further:

"In cancer of the lungs the effects of tobacco smoking are more difficult to prove but there is not the slightest question of doubt as to the fact that those who practise inhaling certainly drive the smoke into the innermost recesses of the lungs. The

> observed increase in cancer of the lungs during recent years is highly suggestive of its correlation to the immense spread of cigarette-smoking habits. In the English statistics the mortality from cancer of the lungs for 1927 was at the rate of 26.8 for men and 9.7 for women. Here again the disparity in sex susceptibility is highly suggestive of smoking habits as a causative factor. But cancer of the lungs has been attributed to a variety of modern conditions which may account more or less for the observed increase which cannot be entirely, at least, attributed to better diagnosis. In England and Wales cancer of the lungs has increased in males from 0.2 during the ten years ending with 1910 to 26.8 during the year 1927. In females the rate has increased during the same period from 7.0 to 9.7. Yet smoking habits have proportionately increased faster among women during recent years than among men. But the fact must not be lost sight of that the injurious effects of tobacco smoking in their relation to cancer probably require quite a long period of time to become noticeable. Since I have dealt with the question of cancer of the lungs in a separate discussion published in the American Jornal of Tuberculosis (2911), I will not enlarge upon it on this occasion, except to say that personally I am strongly of the opinion that a relation between the increase in smoking habits and cancer of the lungs may safely be assumed to exist. I have never been inclined to accept the view that the increase in lung cancers during recent years is chiefly attributable to the after-effects of the influenza epidemic. As observed in the Journal of the American Medical Association of February 13, 1916, the clinical records in a large proportion of the investigated cases did not show any history of influenza." (pages 61-62 of ref. 3131)

Hoffman wrote a monograph on Diet and Cancer, which suggested that he was personally committed to dietary factors in causation of cancer (see Topic E). The prevalence rate of tobacco smoking of non-cancer patients reported by Hoffman, i.e., 42 percent heavy smokers, are comparable to results of Fortune Magazine survey conducted in the 1930's. The question asked was "Do you smoke cigarettes?" without qualifying to heavy or moderate or light. In the Fortune survey, 52.5 percent of all males interviewed answered "yes" which would include heavy smokers and otherwise (3541).

It was apparent that prior to reporting results of a 1939 case control study, the available studies indicated that the prevalence of tobacco smoking

in cancer patients was no higher than that of non-cancer patients and general population. Initial control studies are described in Chapter IV.

Experimental carcinogenesis.

In Harris' SOA report, there were 18 summary statements under the group title of "Experimental and Chemical Studies 1900 to 1947." My general plan is to discuss the opening three statements (4.1 and 4.2), and then proceed to those relating to tobacco tar (4.5 to 4.9). The statements on urinary bladder carcinogen (4.3) and on coal tar (4.4) are discussed in greater detail under Topic D heading of "Occupational and Environmental Factors." Statements summarizing progress during the 1940's (4.10 to 4.18) are covered in Chapter IV. The opening summary statements in Harris' SOA report were as follows:

> "4.1. Scientific articles concerning the potentially cancer-caausing effects of tobacco products on laboratory animals date back to 1900. (See references in Schurch and Winterstein 1935, 1937; Muller 1939; Campbell 1939; Sugiura 1940; Flory 1941; Ebenius 1943; Wynder, Graham and Croninger 1953; Graham, Croninger and Wynder 1957; Wynder 1955; Wynder and Hoffman 1967)
> 4.2. Such experimental attempts to induce cancer in laboratory species with tobacco products were motivated, in great part, by the clinical literature linking tobacco and cancer (e.g., Roffo 1930b, 1937b; Cooper et al. 1932).

Although the Tobacco Monograph (6101), was a reference cited elsewhere in Harris' SOA Report, its authors (Larson, Haag & Silvette) were not included as a reference under the subject of experimental carcinogenesis. I do not agree with Harris because the Tobacco Monograph contained a thorough discussion of publications relating to the above summary statements. Since more than half of articles on experimental carcinogenesis are in Spanish or German, it is

difficult for me to improve or paraphrase the description by Larson, Haag & Silvette, who examined all published articles.

Roffo's rabbit experiments using tobacco. During the 1930's, the most prolific writer on "tobacco tar" as an animal carcinogen was Professor A. N. Roffo, Director of the Institute of Experimental Medicine for Study and Treatment of Cancer of the University of Buenos Aires. There were more than 250 articles published from 1920 to 1935 by Roffo and his associates (see Index to the Literature of Experimental Cancer Research 1900-1935 submitted as Enclosure G). Larsen, Haag & Silvette listed 45 publications of Roffo relating to tobacco and cancer published from 1930 to 1950, and 17 were cited by Harris. Larsen, Haag & Silvette overlooked a dozen articles by Roffo and his collaborators on the subject of experimental skin tar cancer.

Harris, in his SOA Report, summarized the contributions of Roffo as one who applied chemical and biological techniques for studies on "tobacco tar."

> "4.5. In the 1920s and early 1930s, experimental scientists had found that carcinogenic tars could be formed from the pyrogenous products of a variety of organic materials (Kennaway 1925; Kennaway and Sampson 1928; Watson 1933). Given the clinical evidence on tobacco and cancer, it was logical that a carcinogenic tar could likewise be formed during tobacco smoking (e.g., Cooper et al. 1932; Bogen and Loomis 1932; McNally 1932).
>
> 4.6. Following such logic, Roffo published an extensive series of papers on tobacco carcinogenesis in Spanish, German and French language scientific journals during the 1930s (Roffo 1930ab, 1931ab, 1932, 1936, 1937abcd, 1938, 1939abcd, 1943). Roffo's findings were cited repeatedly in the world scientific literature, including English language journals (McNally 1932; Campbell 1939; Ochsner and DeBakey 1941; Flory 1941; Editorial 1941; Menne and Anderson 1941; Grace 1943, 1944; Ochsner 1945).
>
> 4.7. Among Roffo's experimental findings were: production of oral leukoplakia after exposing rabbits to tobacco smoke (1930a); production of an infiltrative, metaplastic epithelial tumor after 8 months of painting rabbit ears with the water-soluble components of tobacco smoke (1930b, 1931a, 1937d); failure to produce such a

> cancerous lesion by aplication of nicotine alone (1930b, 1931a, 1937d); production of a metastatic carcinoma in a rabbit exposed for 3 years to a jet of whole tobacco smoke (1931b, 1932); production of squamous cell carcinomas in multiple experiments by 8 to 14 months' of application high-temperature, destructive distillates of various types of tobacco (1936, 1937abcd, 1938, 1939ac); induction of neoplasms in rats with implanted pellets of tobacco tar (1936); spectroscopic identification of benzo(a)-pyrene in the tobacco distillates (1937b, 1939bd); production of squamous cell cancers in rabbits after 12 months' application of tars prepared from condensed tobacco smoke (1939e); and production of lung cancer in rabbits after direct injection of tobacco distillate into the lung (1943)."

The most important criticisms to Roffo's group of articles are: (a) The publications were repetitive in contents; (b) Rabbits were used, instead of mice and rats used by European and North American researchers on coal tar skin cancer, and by Roffo himself on ultraviolet skin cancer; (c) The publications citing Roffo's work did not exceed twenty, including the nine mentioned in Harris' Summary Statement 4.6. During the 1940's, additional publications by Roffo and his Latin-American contemporaries appeared and are reviewed in Chapter IV.

Beard et al wrote a 1936 review entitled "Experimental Production of Malignant Tumors in the Albino Rat by Means of Ultraviolet Rays." It is necessary to recall the research conducted by Roffo that started in 1916, so:

> "Roffo has been interested in the cholesterol content of neoplasms for many years. In 1916 he showed that a rat tumor may contain over twice as much cholesterol as is found in the whole organism of the host. The normal skin of the face may contain three to six times as much cholesterol as that of the abdomen. It was further observed that the large amount of cholesterol in the face resulted from the exposure to sunlight. Roffo and Pilar then exposed rats to sunlight and ultraviolet light. Increases of 23 to 100 per cent in the cholesterol content of the skin occurred. It was suggested that cholesterol prepares the soil for subsequent malignant growth by acting as an accumulator of light.
>
> Further work by Roffo is interesting in this connection. He exposed rats to ultraviolet irradiation, beginning with a five-minute daily dose, which was gradually increased to twenty hours daily. The latter dose was given from six to eight months. Tumors on the eyes, ears, and back of the head were produced. Later

600 rats were exposed to direct sunlight for five hours. Of these, 365 died of sunstroke in a day; 165 of the remaining 235 developed tumors within ten months. The animals were fed a stock diet of bread and milk. The areas affected were those unprotected by hair, and the histologic form differed with the seat of the tumor. Spindle-cell sarcoma developed on the conjunctiva of the eyes and carcinoma on the nose and forefeet. Of the tumors on the ears, 58 per cent were carcinoma, 36 per cent spindle-cell carcinoma, and 6 per cent carcinosarcoma, while on the eyelids 50 were carcinoma and 50 per cent spindle-cell carcinoma. From the results of experiments with rays from different sources, the cancer-producing action is believed to depend more on the actinic intensity of the ultraviolet wavelength than on the quantity of rays. Local hypercholesterolemia was noted one day after exposure and before any skin lesions appeared.

Findlay exposed 20 mice to ultraviolet rays after removing the hair from certain areas with sodium sulfide. Typical epitheliomas were produced. Similar results have been obtained by Herlitz, Jundell and Wahlgren, using white mice. Putschar and Holtz also obtained epitheliomas of the ears under similar conditions without depilation. They believe that there are close histologic relations between ultraviolet ray cancer and the precancerous light dermatoses that may occur in man, and are convinced that their experiments show the etiologic role of ultraviolet rays in skin cancer in human beings.

Roffo next exposed rats and mice to the entire range of solar rays for a period of nine to ten months and produced typical carcinomas and a fusocellular type of sarcoma. An epithelioma of the ear began as a hyperkeratosis which at the end of about eight months' exposure had developed into a typical carcinoma. The sarcomas usually developed without prceding into a typical carcinoma. The sarcomas usually developed without preceding keratosis. There were 140 tumors on the ears, 58 on the eyes, and 15 on the paws. Histologically the eye tumors had the appearance of a spindle-cell sarcoma. Roffo stated that a biochemical change in the form of a hyper-cholesterolemia takes place as a result of the exposure to the ultraviolet rays of the sun. This results in the transformation of the normal into a neoplastic cell.

Much publicity was given to Roffo's report, and the Academy of Medicine of Paris appointed a committee consisting of Roussy, Hartmann and Beclere to verify the above findings. Roffo's work was confirmed, and the potential danger of excessive exposure of the individual to sun baths was stressed by this committee." (pages 258-259 of ref. 3637)

It should be noted that Roffo's controversial work on rat skin cancer was later indicated. His work on rabbit skin cancer continued to be a controversy

because subsequent investigators used mice and rats, just as Roffo did in his experiments using ultraviolet. It is not clear to me why Roffo used rabbits in his "tobacco tar" experiments.

Harris defended the above Summary Statements in his Oral Deposition, Transcript of Trial Proceedings, and Experts Responses to Requested Information (ERR pages 26-28). Roffo's accomplishments were defended by Harris, and enumerated the authorities who subsequently agreed with the original findings that tobacco tar painted to skin of experimental animals caused new growths. There were criticisms of Roffo's technique that appeared in the 1940's and the 1950's but they were ineffective because of additional positive findings in mice and rats that were essentially similar to results of Roffo's rabbit experiments. I recommend that a trilingual expert, preferably an epidemiologist (like Najera) be requested to review all publications of Roffo, all conflicting articles on experimental pulmonary carcinogenesis, and the relevance of experimental skin carcinogenesis to human lung cancer. Until a trilingual expert can complete an evaluation of Roffo's experiments, I suggest that the following summaries prepared by Larsen, Haag & Silvette be used:

> "An extensive study of 'tobacco' carcinogenesis in the rabbit was begun by Roffo about 1930, and continued for a dozen years and more. In some of his earliest experiments, he gave rabbits daily injections of tobacco-smoke into the gum, and after 25 days, observed lesions with the characteristics of a plaque of leukoplakia at the site of application (3034, 3035). He ascribed this result to the action of the resinous substances produced by pyrogenous distillation. Previous daily injections of a colloidal solution of cholesterol were said to shorten the period of tobacco treatment before the appearance of leukoplakia. This author then investigated the carcinogenic effect on the rabbit ear of tobacco-smoke (3228, 3229), tobacco-smoke solution (3036, 3127), and various preparations of tobacco tar produced by destructive distillation (3646, 3731, 3733. 3847. 39346, 4316), and also from tars similarly prepared from coffee (3940, 3941), tea (4012), and yerba mate (4111). The incidence of cancerous lesions in these

experiments is shown in Table 13-1. The characteristics of the tumors produced were described in detail, and photomicrographs reproduced (3034, 3228, 3646, 3733, 3940, 3941, 3946); and in summary, Roffo (3945) stated that the evolution of the lesions was more or less the same with all the tars, including non-tobacco tars: the lesions began with hyperkeratosis and papillomas which, within 9 or 10 months, changed to infiltrative Malpighian epitheliomas, with invasion and destruction of the organ; the histological type was that of a prickle-cell carcinoma presenting sometimes a marked anaplasia. Although tars produced from coffee, tea, and mate were found to be as carcinogenic as tobacco tars, Roffo pointed out that the former substances presented no danger, since they were prepared as infusions in which tars are insoluble. Coal-tar produced the same carcinomatous tumors on rabbit ears as tobacco-tar, but the latter was said to be more active (in contra-distinction to comparative results obtained by many investigators on mouse skin), and animals which tended to be resistant to tobacco tar were also resistant to coal-tar (4013). All but one of the tumors produced by application of tobacco-tar to the ear of rabbits (the figure of 1000 animals is given, but this apparently refers to the total number of animals used, rather than to the number of tumors found) were said to have had an epithelial histo-pathogenesis, the exception being the production in 1 animal of a tumor corresponding to the histopathlogical type of fusocellular sarcoma, demonstrating the capacity of tobacco-tar to exert a carcinogenic action on the connective tissue as well (4212). A malignant and metastasizing carcinoma was described in great detail (4312, 4315, 4412), and still another malignant tumor was the subject of a special description (4314). Before leaving the subject of Roffo's animal experiments, it should be mentioned that this author did not appear to use pure strains of animals, and that the incidence, if any, of spontaneous ear tumors in control animals was unknown or unreported. Thus, the 'production', by tobacco-tar application in only 1 animal out of 1000 of a 'sarcoma' or of 1 or 2 apparently extraordinary malignancies, may, for all one can tell, be within the incidence-rate of spontaneous tumors; it seems clear, however, that such tumors were not produced in any scientific or experimental sense of the word; and one must therefore be very hesitant in placing too great weight on Roffo's reiterated description of a solitary tumor.

Roffo (3646, 3733) tested the carcinogenic properties of 3 fractions derived from the destructive distillation of tobacco, the first between 100-120°C., the second between 120-135°C., and the third consisting of the residue from this distillation. The second product was considered to be the most active on chronic application to the rabbit ear, 15 or 16 rabbits surviving for more than 7 months having developed tumors from product 2, and 70% of 20 animals from product 3 (3733). Oil distilling above 380°C. from tar obtained by destructive distillation of dry tobacco leaves also uniformly produced malignant tumors when painted on

the ears of rabbits (3948). All tobaccos in commerce yielded the same type of carcinogenic tar (4015). As judged by the carcinogenic effects of chronic application of the 120-350°C. fraction to rabbit ears, carcinogenic potency was greatest for tars derived from Turkish, Egyptian, Kentucky, and chewing-tobacco, and less for tars derived from Havana, Italian, Corrientes, Paraguayan, German, and Salta tobaccos, although even the latter produced at least 50% tumor formation (3944, 3945, 3947). Light tobacco produced a larger quantity of tar than black tobacco, and the tar was also more toxic; but both produced about equal percentages of cancers in treated rabbits (3848). Red tobacco produced a larger quantity of tar than black tobacco, and the tar was also more toxic, although both produced tumors in 80-90% of the animals tested (4011). Exhaustive extraction of tobacco with organic solvents (alcohol, chloroform, acetone, petroleum ether, paraffin, and benzene) prior to the preparation of tobacco-tar resulted in products which showed little carcinogenic activity (4213). Tobacco-smoke filtered through water (with a narghile) or through cotton still yielded a carcinogenic tar, although the latter was less in amount that with unfiltered smoke (3943). Roffo (4213) felt that the precursors of the carcinogenic tobacco-tars were chiefly phytosterols, and these could be extracted from tobacco by organic solvents, and the tar produced by combustion of such extracted tobaccos was relatively non-carcinogenic. This concept was said to be supported by the quantity of phytosterols in tobacco leaves (about 0.53% of the dry matter in black tobacco, and 0.78% in light tobacco), a quantity which is rather high in comparison with the extracts obtained from other plants entering into the human diets (e.g. 0.15% in potatoes, 0.12% in cabbage, 0.20% in oats, and 0.16% in pumpkins). Roffo (3942, 4211) described the isolation of a product from tobacco tar which displayed the spectrographic and fluorescent properties of 1,2-benzpyrene, and presented all the physiochemical properties of the synthetic substance; experiments on rabbits demonstrated that this product was strongly carcinogenic." (pages 422-424 of ref. 6101)

In most of his publications, Roffo recalled the high prevalence of tobacco smoking in cancer patients in general, and in those with oral, laryngeal or lung cancer in particular. Although all of his articles were in Spanish, French or German, most of them contained a summary in English. There is a brief article entitled "Universal Toxicomania of Tobacco" (4115) that was presented as an exhibit during Harris' deposition (pages 420-429, DTH). The 3

pages of text and illustrations have appeared in several of Roffo's scientific publications. Where did this 1941 article come from? What Journal? All of Roffo's articles dated 1940 and later are submitted as part of Chapter IV. Prior to availability of Chapter IV, it is pertinent to quote comments in a 1941 article:

> "The tobacco tar and the coal tar, if applied on the ears of rabbits, produce both the same carcinomatous tumours.
>
> On studying the tumoral lesions developed in these animals, one states that the neoplastic growth is more active, and consequently more malignant, in the ears of tobacco treated animals than in the coal tarred ones.
>
> This observation can be made at simple eye-sight, the tobacco tumours being much more voluminous, cellular and numerous, while those provoked by coal taring are more papillomatous and of marked cornification.
>
> In the present experimentation, we wish to point out a very interesting fact in relation to the biological ground; it is the steady relation of tumour production in both ears.
>
> The rabbits 1, 2, 4 and 5 and especially 7, show, for instance, a strong quantitative resemblance of their tumours production in both ears. The last mentioned one presents a very abundant tumour production, on one ear as well as on the other, while in the animals 8, 9 and 10 this production is a most limited one; in fact, we did not observe on each ear of these animals more than 1 or 2 minute papillomata.
>
> This phenomenon once more proves the importance of the biological ground in the cancerization of tissues, in the presence of a carcinogenic agent; the animal which has a biotissular predisposition, has it for one ear as well as for the other.
>
> On the other hand, there is another remarkable result which is in relation with the focus of cancerization under the direct action of a carcinogenic agent because the cancerization of one ear by one of these does not necessary exclude the cancerization of the other by one of those, providing that the host has a constitutional inclination towards cancerization.
>
> The experimental fact is related to another one which I already published in 1916, in a communication on my experiences with transplantable tumours in white rats.
>
> I described there that on inoculation of the same host with two grafts of the same tumour both develop in the same manner; and even if the grafts were taken from histologically different tumours, their development is alike, although each conserves the histological structure of the respective primary tumour.
>
> Moreover, the present experimentation establishes the carcinogenic unit of all the tars in general, of whatever origin they may be.

> I already studied this matter in an earlier paper in connection with the carcinogenic unit of all the ears extracted from different tobacco types, a study which has been completed lately by experiments with coffee and tea tars.
>
> All these tars present the same physico-chemical characters as the coal tar, especially as to the spectrography and fluorescence." (pages 1011-1012 of ref. 4116)

The above article, with an English summary, was one of several missed by Larsen, Haag & Silvette, and also by Harris. During the 1940's, the techniques used by Roffo for identification of benzo(a)pyrene was criticized. However, the identification of benzo(a)pyrene in tobacco tar by other investigated has muted the question whether Roffo used an acceptable procedure.

Additional rabbit experiments. Prior to and during the 1930's, seven laboratories tested tobacco tar on rabbit ear with essentially negative results. The description by Larsen, Haag & Silvette was as follows:

> "In the [apparently] earliest reported experiments on rabbits, Wacker and Schmincke (1101) obtained tobacco-tar by washing heavily tarred smoking-pipes with alcohol, then evaporating the alcohol and dissolving the residue in fat or oil, or else steam-distilling the residue and treating it with ether before preparing an oily solution. They injected this substance into the ears of rabbits, and noted that extensive growths resulted, histologically resembling very strikingly squamous-cell carcinoma. Helwig (2720, 2827) duplicated the work of the preceding investigators, but reported that, although an atypical proliferation took place, there was never an actual malignant transformation.
>
> Schurch and Winterstein (3542) (see also Schurch 1935, 1936) treated 12 rabbits on both ears twice weekly with nicotine-free cigar-smoke tar for 220 days, but no disturbances of hair or skin resulted. Following this experiment, the same animals had the mouth treated with the tar, 3 times a week for 1.5 years, and again no abnormalities were noted. In rabbits generally damaged by being placed on a high cholesterol diet and by being previously treated with coal-tar on one ear to the point of obvious changes, tobacco-tar painting of the opposite ear produced in some instances tumors and cancer within 1-5 years. The accelerating effect of coal-tar or cholesterol had previously been described by Lu-Fu-hua (3447). Schurch and Winterstein (3734) pointed out the importance of the time factor with tobacco-tar; the cancer-provoking action of tobacco tar was said to be small, but when acting over a long period of time, it may cause more cancers and precancerous lesions

> than most contemporary work would have it believed. The contemporary work referred to by Schurch and Winterstein was apparently that of Bogen and Loomis (3227), Lü-Fu-hua (3447), and Sugiura 1940, all of whom failed to produce any cancerous change in the ears of rabbits painted with tobacco-tar for periods up to 6 months. On the other hand, ear papillomas or cancers were produced by similar treatment with gas-house tar (Bogen and Loomis, 3227) or by coal-tar (Lü-Fu-hua, 3447). Chickamatsu and Katsunuma (3129) appear to have demonstrated a canceroid on the ear of a rabbit produced by continued application of tobacco-tar for 225 days; histologically, this was said to be a typical carcinomatous infiltrating growth; neither metastases nor 'taking' of transplants was observed. [This article appears to be an abstract of a demonstration, and no mention is made of the number of animals treated to produce the one demonstrated lesion]" (pages 422-423 of ref. 6101)

The discussion of rabbit experiments continued through the 1940's. It became apparent a decade later that rabbit ear painting was less favorable for experimental carcinogenesis compared to other animal species.

Experimental carcinogenesis in mice. The first publication on exposure of mice to cigarette smoke was reported by Mertens, from the University Hospital of Munich (3031). The exposure schedule reflected a trial and error approach. Of the 125 mice that entered the experiment, 28 were still alive 22 months later. Some died from convulsive effects of smoke. One mouse developed bronchial carcinoma but Martens doubted whether it was caused by exposure to smoke.

With the exception of Merten's experiments, those conducted by other investigators consisted of applying or painting "tobacco tar" to skin of mice. The technique originally was applied to coal tar for the purpose of identifying carcinogenic substance involved in tar skin cancer in humans. The investigators using "tobacco tar" intended the results in mice to apply to oral cancer but later researchers applied results to lung cancer in humans. The review of

skin painting experiments by Larsen, Haag & Silvette contained the following description:

"A. Leitch (2221, 2322) conducted experiments in which application of nicotine-free tarry material prepared from artificial pipe-smoke to the skin of mice for many months led to epilation and chronic ulceration of the areas of application, but without any neoplastic reaction in a single case. Therefore, he did not consider tobacco-smoke tars a specific irritant of the tumor-producing class.

Helwig (2720, 2827) painted nicotine-free ethereal extract of tobacco-tar from briar pipes on the back of the heads of 50 mice, 3 times a week over a period of almost 1 year. Although ulceration of a rather marked degree was produced, no atypical growth was ever encountered in sections taken at intervals from these ulcers. In further experiments, ether and chloroform extracts of tar produce by distilling tobacco at a temperature of 400-500 C. was applied to 50 mice for about 8 months, and again nothing but ulceration resulted; and, when the painting was suspended, the ulcers healed promptly. No warts were produced. The strain of albino mice used was the low spontaneous-cancer incidence. As a control, typical infiltrating squamous-cell epithelioma was produced with an extract of soot.

Bogen and Loomis (3227) also concluded from their experiments that tobacco-tar did not possess the irritating and epithelial-stimulating properties which lead to the production of neoplastic growths when tested on the skin of mice. Tar obtained by the destructive distillation of Kentucky Burley tobacco in a current carbon dioxide, and then purified by repeated extractions with sulfuric acid, alcohol, and ether, was diluted with equal parts of glycerine, and applied to an area 1 cm. in diameter on the back of the neck of 12 mice twice a week; in this strain of animals, spontaneous tumors had developed in less than 1% during the preceding 2 years. In addition, 12 mice of similar age, sex, and size were similarly treated with gas-house tar of known carcinogenic properties. The mice treated with tobacco-tar showed no marked changes in the skin and no carcinomatous changes, while the coal-tar-treated mice showed marked changes in the skin in a few days, and within a few months, papillomas appeared in almost every case, and eventually metastases appeared.

Hirst 1932, collected tar from tobacco mechanically smoked at 400-500 C. and at 700-800 C., and applied them in concentrations of 10-50% in alcohol, benzene, or glycerol to the skin of the back of the neck of mice at intervals of about 3 days for periods up to 22 months. A tumor developed in only 1 of 50 animals used; and, in comparison with the very high incidence of cancer in mice treated with coal-tar, this indicated to the author that tobacco was relatively unimportant in the causation of cancer.

According to Schurch and Winterstein (3542); also Schurch 1936, tobacco (cigar) tar and its several fractions did not produce cancer in mice, either alone or in combination with mechanical and thermal irritation. Only loss of hair and some skin atrophy at the site of application was noted in 100 animals treated with whole tar containing nicotine once or twice weekly for 258 days, although many animals became ill and died of nicotine poisoning. Similar results were obtained using a thicker preparation of tar over a period of 265 days, and also using a nicotine-free tar headed to 130 C., or when the skin area was rubbed with emery paper previous to the application of tar. No cancers resulted from treatment of mice with various tar fractions having different distilling ranges. No polycyclic aromatic hydrocarbons were found in tar obtained from cigar-smoke, and the cancerogenic hydrocarbons carbons of coal-tar were not present in tobacco tar (3542).

J. A. Campbell (3742) reported painting 24 mice with concentrated tobacco-tar obtained from cigarettes mechanically smoked, twice weekly, and at the time of writing had obtained cancer of the skin in only 1 of these. From a later report, (Campbell (3953)), it appeared that the animals were treated for 20 months, and a typical epithelioma had developed in 1 animal and a typical pre-cancerous hyperplasis in another. Compared to road-tar, the author noted, this tobacco-tar was certainly not very active, but it apparently may give rise to cancer of the skin after prolonged application.

Taki (3737; see also Kinosita, 3711 for details) applied the ether-soluble nicotine-free fraction of tar from tobacco pipes twice weekly to the skin of 104 mice. Of these, 94 died in 110 days or less, and of the surviving 10 which had passed the 130-day mark, 2 showed squamous-cell epitheliomas and 3 showed papillomas; the first papilloma was noted after 85 days. Parts of one specimen of epithelioma showed sarcomatous appearance microscopically, such as is rarely seen in coal-tar cancers; the transplantation of this specimen was successfully accomplished through two generations." (pp 413, 414, ref. 6101)

Similarities and differences between cigarette tar and coal tar, revealed by animal experiments. Although Roffo repeatedly described the similarities between coal tar and tobacco tar, other contemporary investigators from Europe and North America disagreed. Schürch and Winterstein from the University Hospital of Zurich, found that distilled fractions of tobacco tar did not contain the polycyclic aromatic hydrocarbons present in coal tar (3542). Unlike Roffo, the Swiss investigators did not observe any carcinogenic

effect on mouse and rabbit skin. Rabbits previously fed with cholesterol-rich food and skin painted with coal tar showed 'tar warts' from topical application of tobacco tar, instead of a malignant invading papilloma.

Cooper, Lamb, Sanders and Hirst from the University of Birmingham, England, conducted their investigation of tobacco tar on mice "specifically in reference to pipe smoking." They reasoned that since there was a well established occurrence of a "carcinogenic constituent in gas works tar", the possibility existed that tar formed during tobacco-smoking is causally associated with cancer of the lip, tongue, or throat (3230). Tobacco tar was produced by igniting leaf at 400-500^{o}C. and 700-800^{o}C. Among over fifty mice painted with tobacco tar and observed for up to 22 months, only one mouse developed epithelioma. They concluded that since only one tumor appeared compared with "the very high incidence of cancer in mice treated with coal tar, tobacco is relatively unimportant in the causation of cancer." The fluoresence spectrum of tobacco tar was diffuse (4400 to 4600 Au) unlike carcinogenic substances from coal tar that have distinct bands (4000, 4180, 4400 Au).

Experimental carcinogenesis in rats. During the 1930's, the rat was not used for skin painting. Instead, the rat was used to test carcinogenicity of tobacco extracts injected into tongue, gastrocnemius muscle or lung tissue, implanted as a pellet in the urinary bladder, or administered orally. The description by Larsen, Haag & Silvette was as follows:

> "Morpurgo (3557) made repeated injections of small amounts of an extract from the tips of strong-smoked cigars [details of preparation not stated] into the tongue and gastrocnemius muscles of a strain of white rats in which spontaneous tumors of the muscular tissue had never been observed. In 9 or 10 of such experiments, injection into the tongue was followed by a severe, extensive, and

prolonged inflammation, with necrosis and active regeneration of transversely-striated fibers, the process developing into a severe atropy and lipomatosis of the muscles and the formation of a granuloma rich in giant cells and cysts; in 1 rat, dying after the third injection, a very atypical myoblastoma had formed in the region of the strongly inflamed tip of the tongue. No indication of blastomatous neoformation was ever found in the gastrocnemius muscle.

In 50 white rats fed tar (0.15ml. per 120 gm. body weight) from black commercial tobacco in their ordinary diet, lesions in the stomach were observed in 50% of the animals 5-30 months after starting treatment (Roffo 4112, 4211, 4212, 4214). The lesions began with a simple hemorrhagic ulcer, which later became necrotic, and finally developed into a round ulcer, which became cancerized as the last stage of the process. The cancers produced had the histological structure of adenocarcinoma. The gastric region which suffered most was the glandular zone.

Roffo (3126) placed in the bladder of 10 rats globules of resin in which tobacco-extract had been incorporated, and, in equal numbers of control animals, resin, the distillation product of tar, tricresol, or aniline oil. At the end of 8 months, papillary formations were found in the bladder in all cases. The lesions caused by tobacco were said to be of distinctly neoplastic type. Similar globules placed in the peritoneum and in the subcutaneous tissue of other rats became encysted, and globules placed in the stomach were eliminated. This same author recorded thedevelopment of a pulmonary carcinoma produced locally in a rat at the focus of the injection [apparently repeated] of 1 drop of tobacco-tar mixed with an equal part of bird-lime (Roffo, 4313). At death of the animal in 8 months, a tumor the size of a lentil was found in the upper lobe, and similar but smaller formations were distributed throughout the rest of the lung; histologically, the process presented the structure of a pavement carcinoma with horny globules.

Roffo (4211) claimed to have demonstrated the presence in, and to have isolated 1,2-benzprene from tobacco-tar, and the carcinogenic properties of this tobacco benzpyrene were said to have been demonstrated in rats." (pages 420-421, ref. 6101)

There were no control animals injected with substrate excluding tobacco. The question as to whether Roffo detected 1,2 Benzpyrene (Larsen's et al interpretation) or 3,4 benzpyrene, cannot be answered now because of differences in terminology used by Americans and British chemists during the 1930's. The question is raised again in Chapter IV.

McNally, from Rush Medical College, failed to find tumor in the mouth or the back of rats following topical administration of tobacco tar. Although he did not analyze the tar, he recalled the literature relating to pyridine present both in tobacco tar and in English charcoal briquets (3224).

Bogen and Loomis from Olive View, California, followed his 1929 report on composition of cigarette smoke (2928) with the study of tar application on mice skin (3227). He noted that the cutaneous application of tar derived from destructive distillation of tobacco did not possess the irrtating and epithelial stimulating properties that led to the production of neoplastic growth. Mice treated with gas-house tar developed metastasizing epithelioma.

McCormick, from Toronto, in reviewing some medical aspects of tobacco, commented on alleged carcinogenicity of tobacco:

> " Relative to the effect of tobacco on the digestive and respiratory systems, recent work on the cancerogenic properties of certain hydrocarbon distillates seems of interest. It has long been known that workers who handle pitch, and others who are employed in the manufacture of briquets from pitch and coal dust, frequently suffer from skin cancer. Likewise, shale oil workers coming in contact with crude paraffin, a natural distillation product, and chimney sweeps exposed to soot, a distillation product of coal, are known to be unduly prone to skin cancer. Recently Cook, Hieger, Kennaway and Mayneord (3333), working in England, and Morton, Branch and Clapp, in America, were able to isolate from coal tar certain benzene derivatives, such as benzpyrene, dibenzanthracene and triphenylbenzene, which, when applied to the skin or injected subcutaneously in mice, would produce cancer. This discovery throws new light on the possible role of tobacco in the causation of cancer of the lip, mouth, stomach and lungs, affections notably predominant in males, who in smoking expose these parts to the irritant action of the distillation products of tobacco. Thus it seems that certain products of combustion and distillation of the organic matter of tobacco, aside from the thermal and mechanical irritation associated with smoking, may sensitize the skin and mucous membrane of the respiratory and upper digestive tracts to cancer." (pages 68-69 of ref. 3849)

The topic of tobacco experimental carcinogenesis ends with a reminder to the reader that the original purpose of skin painting experiments was to identify carcinogenic substances in coal tar causing skin cancer in workers exposed to fossil fuel products. The application of tobacco tar experiments to mouth cancer and lung cancer were not accepted by most clinicians, with the exception of the few enumerated above and highlighted in Harris' SOA report.

There was no reported testing of cigarette smoke by inhalation in rats. In later decades, the rat lung became preferred experimental model for long term testing of suspected carcinogens and also to examine biochemical, functional and microscopic changes in carcinogenesis. After decades of testing in rats, there has been no positive results from long term cigarette smoke inhalation in rats.

D. OCCUPATIONAL/ENVIRONMENTAL FACTORS

During the 1960's, it became apparent to government toxicologists and their consultants that occupational and environmental health hazards can be derived from the same human and animal studies. I have therefore adapted the terminology of occupational/environmental factors, although information was derived from workers or general population. Harris described etiologic factors other than tobacco smoking and are covered by the following blanket statements:

> "4.3. During the 1920s and 1930s, experimental scientists increasingly recognized that specific chemicals or mixtures of chemicals could cause cancer. Moreover, the scientific community increasingly acknowledged the complementary roles played by experimental studies in animals and clinical observations in humans. For example, epidemiological studies of bladder cancer among aniline dye workers ultimately lead to the experimental induction of bladder cancers by the chemical beta-naphthylamine in 1938.
>
> 4.4. Similarly, Passey's (1922) experimental finding of the carcinogenicity of soot extracts confirmed the frequent clinical observation of cancer in soot-exposed workers. Likewise, clinical observations of skin cancers in coal tar and pitch workers stimulated a detailed study of high-boiling fractions of coal tar distillates (e.g., Kennaway 1925). By the early 1930s, such studies had lead to the identification of at least two specific chemical carcinogens, dibenzanthracene and benzo(a)pyrene. (See references cited in Berenblum and Schoental 1947; U.S. Public Health Service 1964.)

Should counsel decide to present another expert witness, the above statements can be criticized briefly as follows: The 1938 episode relating to bladder cancer involved Hueper, the posthumous expert I have selected (see page 7). The clinical and laboratory studies on coal tar during the 1930's far exceeded those for cigarette smoking.

Urinary Bladder Cancer.

The lack of a reference for Harris' SOA statement 4.3 was probably an attempt to minimize the contributions of Hueper in the field of occupational/ environmental cancer, and to wrongly characterize him as one who participated in a "critical counterattack" of the evidence that smoking caused lung cancer [SOA 6.15]. Hueper was accredited to have conducted the key experiment that proved administration of beta-naphthylamine caused bladder tumors in dogs (3850, 3851). He reviewed the complex literature (3450) prior to the experimental study and retrospectively reviewed how positive results in animals answered etiologic questions in human bladder cancer (3852). Hueper was respected by other researchers in aniline bladder cancer (3761) that included Henry, Kennaway & Kennaway (3128) who were also interested in coal tar cancer. It was rumored that Hueper left DuPont (3735) because of disagreements on publishing the results of key dog experiments.

Hueper wrote on other topics relating to chemical carcinogenesis such as: growth factor (3311, 3449), immunologic aspects (3231, 3448, 3639), tuberculosis (3045), neoarsphenamine (3332), polyvinvyl alcohol (3950), and ethylene glycol (3640, 3853). Some publications relating to host susceptibility to cancer are discussed under Topic E while industrial chemicals are discussed under Part Four as they relate to tobacco smoke constituents. Hueper did not publish articles on environmental factors, tobacco smoke and lung cancer during the 1930's although his earlier articles (2633, 2933) were cited by contemporary authors (3761).

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Lung Cancer Monographers.

As a general rule, monographers accepted the role of occupational/environmental factors in pulmonary carcinogenesis, more than that of tobacco smoke. Although all monographers favored the occupational/environmental etiology, some of them did not mention tobacco smoking.

Ewing: Neoplastic Diseases. This was a treatise on pathology and clinical aspects of all forms of tumors. The etiology section in the chapter entitled "Tumors of the Lung" included:

> "In mice that had inhaled road-dust containing from 2 to 3 per cent. of tar, Campbell observed a tenfold increase of adenoma of the lungs. Dust freed from tar gave much less increase, while cigarette-smoke and motor-gas gave a slight increase. Tobacco-smoke is especially incriminated by Roffo, who found spectroscopic evidence of phenanthrene in tobacco extracts, which produced a high proportion of papillomas of the skin. Lehmann found that smoking a 5-gm. cigar yields 200 mg. of inhaled tar, while an 8-hour drive 32 feet behind an automobile over a tarred road yields only 1.5 mg. of inhaled tar. The proportion of smokers among patients with lung cancer is very high (Roffo).
>
> Kennaway found no occupations to which the recorded increase of lung cancer could be attributed. Rural workers are as much affected as urban. Cotton-spinners who inhale air sprayed with an oil which produces cancer of the skin show a small incidence of lung cancer. Craver noted occupations causing exposure to various irritating dusts in 23 per cent. of his cases, and a history of marked previous respiratory infection in only 12 per cent." (page 873 of ref. 4001)

Ewing's bibliography had no listing for Lehmann and Roffo, indicating that the sentences must have been added to page proofs and could not be inserted into the run-on style of references. The paragraph on Kennaway did not reflect the fact that Campbell (preceding paragraph) favored occupational cause of lung cancer. Details of conflicting observations are discussed below. It suffices to reiterate that Ewing had not conducted research on lung cancer and favored theories in earlier editions which he subsequently retracted. Ewing passed

away three years later and there was no subsequent opportunity to correct or revise the above statements.

Monographer (k) Fried: Primary Carcinoma of the Lung. The etiology section in this monograph (3201) also appeared in a review article (3101). The discussion was entitled "Inhalation of Tar Products:"

> "The role of chemical substances in the causation of epithelial malignant tumors was noted by clinicians before the advent of the experimental era of cancer formation. Older observers attributed epithelioma of the lip of pipe-smokers not only to the mechanical action of the pipe but to the tobacco as well. Similarly arsenic, anilin, paraffin, and many other substances were regarded as being carcinogenic by virtue of their chemical composition.
>
> The carcinogenic action of tar was for the first time demonstrated by Ichikawa and Yamagiwa (1513). These authorities have shown that when the rabbit's ear, which is never the seat of a spontan- eous tumor, is painted for a certain period of time with this chemical it develops a malignant tumor. These experiments have since been broadened and successfully applied in the causation of cancers of other structures in different animals, of which the mouse is the animal of choice. The customary technique consists in the application (painting) of tar to certain cutaneous areas, the applications being spaced at short intervals. The intimate mechanism of the neoplastic formation is not understood. With the microscope one notices damage to the skin caused by the chemical followed by excessive regeneration ending in malignant disease.
>
> An outstanding example of pulmonary neoplasms caused by chemical substances is frequently referred to in studies of the so-called "Schneeberger Pulmonary Cancer." The disease is reported to have occurred in a high percentage of workers in cobalt mines in the province of Saxony, Germany. While some investigators attributed the pulmonary new growth to inhalation of arsenic and cobalt, another group was inclined to regard the cancer as being due to chronic inflammatory changes in the lungs caused by the inhalation of dust, and so on. In fact, the incidence of the pulmonary cancers in the Schneeberger inhabitants has recently decreased, apparently as a result of improved hygienic conditions of the mines.
>
> An etiologic relationship between tar and primary bronchiogenic cancer in man was suggested by the reports of Möller (2423), and of Murphy and Sturm (2520). Möller, from Fibiger's laboratory, by painting the back of young rats with tar failed to obtain a cancer of the skin but found that all the experimental animals developed bronchiogenic cancer. Murphy and Sturm have obtained similar results with mice. They, too, have observed that

the external application of tar to a number of separate areas on the surface of mice, in such fashion that no single area is irritated sufficiently long to cause lesions of the skin, has resulted in a very high incidence of typical epithelial pulmonary neoplasms, identical histologically to those found spontaneously in mice. Their previous experiments with transplantation of cancer had shown that repeated application of tar greatly reduces the animals resistance to cell growth. They believe, therefore, that the tar acted apparently only as a factor in lowering the resistance of the mice, while the pulmonary cancer was due to irritation by inhaled dust or particulate matter. (The mice lived in burrows under sawdust and shavings mixed with choped hay.)

Following the reports of these observers a few clinicians have, nevertheless, connected the claimed increase in pulmonary cancers with the modern application of tar to roads. Stäehelin (2526), Heilman (2528) and others suggested that tar, gasoline, and other substances used by automobile cars act in all probability as chemical irritants upon the bronchial tree, leading to epithelial malignant disease. Kimura (2321) claims to have produced pulmonary cancer by injecting tar into the trachea of laboratory animals. His experiments should be accepted with reservation, however, since only one rabbit and one guinea pig were used.

Smith (2826) by exposing mice to coal tar fumes, to fumes from the exhaust of an automobile, and also by painting the rodents with gasoline for a period of five months, could not produce carcinoma of the lungs in the coal tar series; it occurred once in 26 mice exposed to exhaust, and once in 29 mice painted with gasoline. This proportion, according to Smith, is not greater than the laboratory spontaneous occurrence of primary pulmonary cancers ordinarily found in white mice.

It is not at all certain that the alleged increase in the incidence of pulmonary cancers coincided with the inauguration of the custom of painting the roads with tar. Moreover, in Russia, where the primitively-built roads are not painted by tar, and where the number of automobile vehicles is infinitesimal, Davidoff, Uspensky and others have noted a marked increase in bronchiogenic cancers in the last ten years. It would appear, then, that the supposed recent increase in bronchiogenic cancers cannot be regarded as being the result of painting of roads with tar or its products." (pages 22-25 of ref. 3201)

The most important paragraph related to the evolution of concept that lung cancer appeared in mice skin-painted with coal tar. Fried favored the earlier available explanation that coal tar reduced animal resistance to cell growth. Before the decade was over, Andervont described for the first time that a pure

chemical substance, applied to the skin or administered orally or by injection causes lung tumor, and that the susceptibility was influenced by cross-breeding. It is important to start recalling this series of experiments that were widely known in the 1930's, 1940's, and 1950's, but were overlooked in the 1960's to the present.

Monographer (d) Hruby & Sweany: Primary Carcinoma of the Lung, with special reference to incidence, early diagnosis and treatment. There was no mention of tobacco smoke in etiology. The occupational history of patients revealed the following:

> "As to the occupation, there seem to be few instances in which there is any relation to cancer of the lung. Claims have been made that automobile gas, smoke, irritating dusts and tar on roads are contributing causes, but in an analysis of a large number of case histories we were unable to find a tendency in favor of any occupation, trade, profession or station of life. Laborers, office workers, and housewives are most affected, but they are likewise the most numerous. Mechanics, automobile workers, painters, stokers and carpenters are involved about in proportion to their numbers. Perhaps the only instances in which the occupation may be suspected are the cases occurring in certain European mines. Incidence of cancer of the lung was shown by Arnstein to be high in the workers in the Schneeberg mines, but not in the surrounding population. Schmorl and others studied the problem and reported that arsenic is present in high proportions in the dust of these mines. The dust is also said to be radioactive. Pinchan and Sikl showed this in a study of the pitchblende mines of Joachimstal, Bohemia, across the mountains from Schneeberg. These are medical curiosities, however, and produce no great public health problem. Other minerals, such as nickel, cobalt and bismuth have also been accused, but they do not seem to cause any effect when mined elsewhere in the world." (page 507 of ref. 3302)

The role of radioactive gas and dust may have been "medical curiosities", but during the 1980's, there have been some concern on radon in houses in the northeast section of the United States.

Monographer (g) Klotz: Primary Carcinoma of the Lung. In addition to the paragraph on tobacco smoking (see above Topic B), the paragraphs on environmental factors were as follows:

"The development of tarred roads led to much speculation as to a possible etiologic relationship. Some weight is lent to this idea by such observations as those of Kennaway and Kennaway (3632), who noted an increased incidence of cancer of the lung among open air workers exposed to road dusts. It seems remarkable, however, that this observation did not apply to motor vehicle operators who surely suffer a similar exposure. Though a high incidence of lung tumors has been reported from regions where road tarring is not practised, Campbell (3742) does not consider this an argument against an etiologic relationship, stating that dust from such roads may be carried tremendous distances by the air currents. This cannot, however, be considered tenable in view of reports from communities where the injurious agents would have to be carried hundreds or even thousands of miles. Campbell found a high incidence of warts which underwent malignant changes in laboratory animals exposed to dust from tarred roads, but no pulmonary neoplasms developed. Passey and Holmes, carefully analyzing the problem, point out that the alleged increase in lung cancer in Great Britain appeared prior to the tarring of roads. They further suggest that if the time factor required to produce growths in animals, as demonstrated by Campbell, were applied to man, the effect of road tarring should just now be making itself felt.

Fumes from gasoline engines and pollution of the air in industrial centers can be considered under the same category of etiologic agents as dusts from tarred roads. There is certainly no direct evidence to connect lung cancers with the first of these. Though a high incidence of carcinoma of the lung has been noted in some industrial centers where air pollution was great, an equally high incidence has been observed in rural communities. It has also been noted that there is no undue occurrence of the disease among mechanics and garage workers who are constantly exposed to a polluted atmosphere. Although Kimura (2321), reported an adenoma of the lung in a rabbit and an adenocarcinoma of the lung in a guinea-pig following the insufflation of coal tar, Smith (2826), was unable to produce pulmonary tumors in mice by exposing the animals to pitch fumes, products of an internal combustion engine, or by painting the skin with gasoline. Although Smith thus found nothing to support the theory that fumes from coal tar or gasoline were of importance in human cases of bronchial cancer, reports such as that of Kawahata are most suggestive. This investigator observed 12 cases of the disease among employees tending furnaces for gas production, where the air contained several tar derivatives with unknown carcinogenic properties. Recently, Seelig and Benignus (3648) found 8 adenocarcinomata of the lung in

> 100 mice exposed to coal soot, while only 1 tumor developed in their controls. It must be concluded, however, that the evidence incriminating inhaled tar products as a cause of cancer of the lung in human beings is as yet far from convincing." (page 450-451 of ref. 3802)

The conflicting opinions between Campbell and Kennaways relate to workers and environmental pollution in Great Britain. There were differences in ambient air contamination levels but I have not yet found the necessary publications to document my recollection. For pulmonary emphysema, there was a difference in incidence and severity of British and American patients during the 1930's and 1940's.

Monographer (c) Simons: Primary Carcinoma of the Lung. Compared to other moographers, Simons wrote a more detailed review comparing tobacco smoke, street dust particles, motor exhaust fumes, and coal tar partcles. The etiologic reviews relating to each group of inhalants are reproduced completely below to recapture the human and animal studies as interpreted by one monographer, Simons, who, unlike Ewing, conducted original studies on lung cancer.

> "Dust Inhalation. Hampeln (2328) proposed that pulmonary carcinoma is a dust inhalation disease and explained the increased number of these neoplasms as due to the increase of dust produced by the growth of traffic and industry. It was he who directed attention to the fact that in large cities, such as Oslo, where sanitary and hygienic measures were not interrupted by the War but instead were improved by modern technical knowledge, no increase of frequency of pulmonary malignancies has been noted. The difference between Oslo and Riga, where dust constitutes a real menace and where a marked increase in primary cancer of the lung has taken place, he considered proof of his contention that dust is the main etiologic factor.
>
> Not only dust but smoke and chemical impurities in the air have increased along with the growth and concentration of industry, said Heilmann (2528). He showed that the pathologic changes induced by dust in the lungs present a histologic picture, the ultimate sequence of which is carcinomatous. Materna too, considered street dust the prime etiologic factor in pulmonary carcinoma because both have increased during recent years.

Supporting this view, Folgers found pulmonary cancers more frequently in horses, dogs and other animals exposed to street dust than among cattle and others unexposed. Seyfarth (2421) found that men whose vocations expose them to the inhalation of fine solid particles are more often affected than others; this is the reason, he believed, that the right lung is involved most often. Schmorl (2329) insisted that the increase of lung cancers in Dresden is traceable to the sandstone industry and coal mines. Seyfarth denied that any one kind of dust - street dust, stone dust, metal dust, glass or coal dust - can be held solely responsible.

Duguid (2721) reasoned that the single fact that tumors arise in tissues directly exposed to the atmosphere encourages the suspicion that atmospheric impurities may be an important cause of intrathoracic new growths. It must be, he continued, some specific type of pollution rather than general pollution; for the smoke abatement act has cleared English cities of smoke, and hence if intrathoracic tumors were due simply to smoky atmospehere they would have decreased since the passage of that act, which is not true. But they may be due to dampness of the atmosphere causing bronchial catarrah, which may be sufficiently irritating to cause cancer. Assmann (2422) called attention to the frequency of lung cancers in two large cities of Saxony. Especially notable are the high percentages of the Seyfarth (2421) statistics for Leipzig as compared with which Assmann gave the low values of this statistics for Dortmund and referred to the rarity of pulmonary cancer in the Ruhr region and Upper Silesia. He then suggested that it is not so much coal dust in general as dust of the brown coal in Leipzig which should be considered. More recently, the Kennaways (3632), in analyzing 18,280 death certificates of males who had died in England or Wales between 1920 and 1933 as a result of carcinoma of the lungs or larynx, found that a group of open air occupations in which there is prolonged and excessive exposure to the dust of roads has a high incidence of these two forms of cancer.

To the contrary, Berblinger (3134), after examining 12 cases on this point specifically and finding no evidence of chalicosis or anthroacosis in any of the specimens, denied that dust of itself is a cause of lung cancers in any locality. Kikuth (2527) preferred to leave open the question of increased dust in the larger cities, because, regardless of its quantity, it has changed in quality, at least in respect to a relatively higher mixture of benzene fumes. He believed that street dust plays no great part in the etiology of pulmonary cancer, pointing out that there has been an appreciable increase of lung tumors in Jena, a small city with little increase of traffic. Rare discoveries of secondary pneumonoconiosis in pulmonary carcinomas, as reported by Siegmund and Helly, did not impel Probst (2732) to assign a leading role to street dust as a cause of lung cancers. His material demonstrates that teamsters, street workers, policemen, chauffeurs and other

workers especially exposed to street dust show no high incidence of lung tumors.

Thus far, then, street dust has not been demonstrated to be of great importance in causing pulmonary carcinomas. But it may be conceded to be a contributing factor and, in some instances, even the primary etiologic agent. If it is emphasized as a cause, that can be only through its character as a chronic mechanical or chemical lung irritant." ((pages 77-79 of ref. 3702)

Simons, as a thorough and meticulous monographer, reconciled conflicting observations by grouping dust inhalation studies, regardless of whether there were any chemical irritants. In the above discussion, the remarks refer both to occupational exposure of miners as well as to non-occupational or ambient air exposure of general population. The next discussion on motor exhaust fumes refer both for workers, i.e., chauffers, bus drivers, garage operators, tunnel guards, and the general population exposed to motor vehicular exhaust.

"Motor exhaust fumes. Duguid (2721) mentioned the exhaust gases of motor drawn vehicles as possible causes of pulmonary cancers, and Klotz said: 'It is true that the incidence of carcinomas of the lung shows a parallelism with the increased use of automobiles' (2722). According to Heilmann (2528), the exhaust of internal combustion motors and smoke with its by-products are related to tar, whence one may ascribe to them an influence of bronchial mucous membranes already damaged by chronic irritation. But Bloch and Widmer proved that active fractions of coal tar under 230 degrees and 1-2 mm. mercury pressure (the equivalent of 480 degrees normal pressure) contain no, or in all events few, carcinogenic ingredients.

The substance of Probst's (2732) exhaustive treatment of this topic is as follows: The question is whether or not auto exhaust gases contain substances similar to the coal tar derivatives. Data supplied by Professor Schlapfer, director of the laboratory for combustible material at the Union Technical High School, Zurich, show that tars obtained from petroleum products during the process of combustion have an aromatic character only when the disintegrating temperatures reach 900 degrees or more, which seldom occurs in the cylinger walls of gas motors. He reasoned, then, that aromatic combinations with high boiling points such as are found in coal tars do not originate in the internal combustion motors, while it follows that their exhaust gases contain no combinations related to the coal tar products or derivatives with which cancer was produced experimentally in animals. Probst proceeded to state that the traffic of Zurich refutes the views of

> Heilmann, citing the table placed at his disposal by the Bureau of Motor Control of the canton of Zurich. Comparison of these figures with those on the frequency of incidence of pulmonary carcinoma in that locality bears out his position. Further, he recalled that motor traffic was greatly curtailed during the War by shortgage of fuel and that it was during this period that an increase of the disease occurred. Finally, in the vocational data on his cases, no patients were found to be especially exposed to motor exhausts, as are automobile mechanics or chauffeurs.
>
> The case against the motor car, said Passey and Holmes (3537), is supported by two schools, one of which blames exhaust fumes while the other holds tarred roads responsible. But neither garage workers on one hand, nor professional drivers on the other, are especially prone to develop pulmonary neoplasms. In 1936, Schmidtmann, of Stuttgart, reported that the waste gases from gasoline motors have no effect on the bronchial mucosa even after many years of exposure, whereas gases from oil-driven motors cause marked dust deposits with callus formation of the lungs, destruction of the bronchioles, emphysema and symptoms of atelectasis. No infiltrating epithelial growth has yet been observed.
>
> While the belief that there is a causal relationship between motor exhaust gases and pulmonary cancer is alluring, it lacks sound proof." (pages 82-83 of ref. 3702)

Since most of the discussion reviewed vehicular traffic in European cities, I have not obtained all foreign references but selected a few, identified by a four-digit bibliography number.

In the United States, prior to the passage of the Clean Air Act of 1970, there was considerable literature that has convinced me that Simon's statement can be revised as follows: Causal relationship between motor exhaust gases and pulmonary cancer was not only alluring during the 1930's, but was also supported by several human and animal exposure studies prior to 1970.

> "Inhalation of tar particles. In discussing tar particles in etiology, Katz (2731) said: 'How far tar, in the form of auto exhaust gases and street tarring, plays a role cannot be decided at present, since it has been established that tar represents an aspecific or only a relatively specific irritant. Automobile traffic has increased enormously during recent years, but whether the tar derivatives or street dust are to be blamed in our problem cannot be said. City dwellers do not predominate in my series of

cases. The question depends on finding out whether such irritants are, in general, favorable to cancer formation or whether tar derivatives play a leading role in this respect, and finally, whether they are of special significance in the origin of carcinoma of the bronchi. Naturally, that must be though of, since the air passages are particularly exposed by inhalation to many street-borne irritants. Experimental work was done by Brandt, but he could observe only a resulting effort toward regeneration, early signs of malignant growth of the basal cells and bronchial mucous membrane, and not a clearly defined indisputable cancer.'

It is the importance of tar in the experimental genesis of lung cancer that necessitates its consideration here. Möller (2423) painted the backs of young rats with it and obtained the cornified squamous epithelial variety of lung carcinoma in all animals that survived 300 days of painting. He considered two possibilities - that the carcinogenic particles could have traveled either by the blood stream or by inspired air - and then he mentioned hematologic origin of the bladder cancer of aniline dye workers. To a certain extent the work of Murphy and Sturm (2520) corroborates Möller's results (2423), yet the conclusions drawn differ. The former painted the skin of white mice over ever-changing areas for a long time, and thus in two series produced approximately 60-78 per cent, respectively, of multiple epithelial tumors. These tumors were exactly similar to the spontaneous cancer of the lungs of mice which had been characterized by different authors as adenocarcinoma, papillary cystadenoma and adenoma. These authors did not believe that the tumor was transmitted from the skin or that it was caused by tar licked in and resorbed through the intestines but that the application of tar to the skin lowered the resistance to carcinoma and the subsequent inhalation of foreign irritating substances such as hay dust or saw dust led to carcinomatous, cellular proliferation. Febiger, Kennaway, Dreyfuss and Bloch obtained lung cancers by painting white mice for a long time with tar fractions. Kimura (2321) was able to produce pulmonary cancer in one rabbit and three guinea-pigs through insufflation of tar through a tracheo- tomy tube. The case of von Meyenburg is clinically interesting in this connection. The patients, a hairdresser, developed pulmonary cancer after having been engaged for some time in the manufacture of tar soap. These facts point attention to a possible relationship between street-tarring and lung cancers.

Jamagiva said that the increase in lung neoplasms may be attributable to tar dust of roads and streets. Heilmann (2528) referred to the possible dependence of bronchial cancers on the effects of particles of tar, oil and other substances raised by automobile traffic. Bloch's work with Dreyfuss showed that fine dust particles found with varying frequency in different tars must be kept in mind in this connection; the former of these authors, addressing the Swiss street workers' union in 1924, emphasized tarring of streets as a cause of cancer of the lungs. Goltz

(3030) contrasted the annual use of half a million tons of tar on the roads of the United States with the fact that in Hong Kong none of it is used and cancer of the lung is a rarity. Simpson (2927), too, regarded the rarity of lung cancer in Hong Kong and in Singapore, where also no tar is used, as suggestive, for, he said, both clinically and experimentally it is known that tar is a potentially carcinogenic substance.

To refute these suggestions, Konrad and Franke (2955) denied that the increase of the disease in Riga is due to either an increased number of automobiles or an increased use of tar, since neither of these increases has taken place. Probst (2732) concluded, from data furnished by the engineer for the canton of Zurich and the street inspector of the city of Zurich, that road tar exercised no influence on the incidence of pulmonary new growths. Husted and Biilman (3724) were unable to demonstrate relationship between the frequency of pulmonary carcinoma in Denmark and the more extensive tarring of roads. Jaffe (3516) recently pointed out that pulmonary cancer is very common in countries where road tarring is little used, as, for example, in Russia. No evidence could be found by the Kennaways that tarring of the roads has affected the incidence of pulmonary carcinoma in the general population. Such data as are available suggest that coal tar in the atmosphere, whether derived from roads or from any other source, does not readily cause cancer of the lung. Furthermore, an investigator who has exposed mice to an atmosphere highly contaminated with road dust containing two per cent of tar found no pulmonary carcinoma among his animals, even though malignant tumors did arise in the skin.

Also in Basel, Staehelin (2526) found that increased frequency of lung cancers was disproportionate to increased tarring of streets. There, street-tarring was started in 1903, lapsed until 1906, when it was increased so that now 42.2 per cent of the street area is tarred. The increase of pulmonary cancers in 1912 might be explained as due to this cause, but were this the case there should have been a noticeable increase since the War; this has not developed. Staehelin further pointed out that the disease did not start to increase in France directly after 1880, when tarring started there, and that though the practice has continued to the present, Ribadeau-Dumas in 1923 mentioned only two to four lung cancers per 1,000 sections in that country. Vincent made a survey which disclosed no positive relation between the disease and the prevalence of street-tarring in France. So Staehelin argued that it is easier to demonstrate a causal relationship between cancer in general and street tar dust than between the latter and bronchiogenic cancer in particular.

It seems sensible to conclude that inhalation of particles of tar taken into the air from streets and roads may be counted among the chronic irritants responsible for pulmonary carcinomas but that it is in no sense their sine qua non cause." (pages 79-82 of ref. 3702)

Presently, it is no longer necessary to measure tar particles directly, but to collect the benzopyrene component. In more comprehensive studies, hydrocarbons and polycyclic aromatic amines are analyzed in detail. The ozone level used as primary pollutant indicators for enforcing provisions of Clean Air Act represent the end results of vehicular emissions and prevailing wind velocity (Part Four).

Occupational Exposure.

Prior to the 1930's, there was significant number of publications on tar skin cancer, both human studies and animal experiments. The human studies on lung cancer associated with fossil fuel products and combustion emission consisted of reviewing occupational history. Duguid (2721) observed that outdoor workers were more represented than indoor workers in a group of 143 lung cancer patients compared to the general population of Manchester. Harris covered the subject of occupational exposure by the following SOA statement:

> "5.3. Beginning in the 1920s, a variety of factors were hypothesized as contributing to the striking rise in lung cancer. These included: the influenza pandemic of 1918; old tuberculous lesions in lung cancer patients; pre-existing bronchitis and emphysema in lung cancer victims; gasoline fumes containing lead; diesel and gasoline-powered automobile emissions; irritant gases used in World War I warfare; soots, tars and other air pollutants from roads, fuel combustion, and various industrial processes; as well as the rise in cigarette smoking. A concentration of lung cancer cases in the mining district of Schneeberg in Saxony stimulated interest in radioactive substances and certain heavy metals as possible contributors. (See Perret 1929; Hoffman 1929, 1931; Ochsner and DeBakey 1941; Kennaway and Kennaway 1936, 1941)"

It should be noted that Harris did not mention Duguid and the almost fifty articles discussed in the next paragraphs and tables. Kennaway and Kennaway

appeared in the above list of references and the discussions starts with this couple.

Lung cancer deaths in England and Wales. Kennaway and Kennaway examined 18,280 death certificates for lung cancer in males from England and Wales from 1921 to 1932 inclusive. A group of open-air occupations, where there was exposure to dust of roads, had rather high ratios for cancer of the lung. Workers exposed to coal gas and tar, and those engaged in preparation and sale of tobacco, tend to show an increased prevalence of cancer of the lung. The observation on tobacco manufacturers has been transposed by some in support of concept that tobacco smoking was a causative factor of lung cancer (3632). Kennaway & Kennaway discussed the quesion whether tarring of roads contributed to increase in lung cancer deaths. The first of seven numbered paragraphs was on the positive results of animal experiments that are discussed under the next subtopic. The remaining six paragraphs were as follows:

> "(2) In spite of the rather high incidence of lung cancer in those occupations where there is exposure to road dust, it seems wholly unreasonable to attribute the recent increase of this disease among the general population to the tarring of roads. For scores of years before this increase began coal tar was being discharged into the atmosphere in the form of soot by the domestic fire in quantities vastly greater than any which could now be derived from the roads. Tarring of roads must undoubtedly increase the amount of dust derived from tar in the air, but this increase appears negligible in comparison with the amount of soot present already. One sees clouds of smoke drifting over any large town, but one does not see any similar clouds of tar-laden vapour arising continually from tarred roads.
>
> (3) The contamination of the air with soot has probably been decreasing, owing to the greater use of gas and electricity, before and during the period when the recorded cases of cancer of the lung have been increasing rapidly.
>
> (4) Moreover, such evidence as is available suggests that coal tar in the atmosphere, whether derived from roads, domestic chimneys, or any other source, does not readily give rise to cancer of the lung. Chimney sweeps, who of all persons are most exposed to soot, have not a very high ratio for lung cancer, and the other

occupations where there is special exposure to the products of the gas-works (gas stokers, gas works foremen and inspectors, gas fitters, Table IX) show an incidence of lung cancer which is from two to four times that prevailing in the general population. This increased liability, though very undersirable, cannot be regarded as a very high industrial risk. It does not even approach, for instance, the increase of risk of fatal cancer of the scrotum which is incurred in the occupations of chimney sweep or mule-spinner.

(5) Cancer of the lung can undoubtedly be produced by an external agent, for the Schneeberg miners show an extremely high incidence. (Out of 154 miners twenty-one died in 3-1/2 years, and cancer of the lung was found in every one of thirteen of these submitted to autopsy, while of the eight not examined post mortem two had given in life strong evidence of the presence of this disease (Rostoski, Saupe and Schmorl, 1926). These remarkable data make all the more distinct the indication that the potency of coal tar products, though seen clearly in occupations where there is abundant exposure to these, is nevertheless of a low order. Corroborative evidence of this low potency is afforded by the case of the mule spinners who show an especially small liability to cancer of the lung although they inhale air sprayed with an oil which produces cancer of the skin.

(6) Two phenomena which might be discussed in relation to the tarring of roads and cancer of the lung are (a) the parallel increase in lung cancer in country dwellers and town dwellers and (b) the greater increase in lung cancer in men than in women. But one can always argue that tarred roaads do, or do not, now penetrate to all parts of the country, or that women, are, or are not, exposed as much as men to road dust, so no useful purpose would be served by any such discussion.

(7) The similarity has been noticed between the curves showing (a) the recent increase in cases of cancer of the lung and (b) the onset of mule-spinner's cancer (of the skin) after 20-25 years' employment in cotton mule spinning (Henry, (2824)), and the suggestion might be made that the sudden increase in cases of cancer of the lung was traceable to the introduction of tarring of roads about 20 years earlier. But, even if one suppose that road dust is active in producing cancer of the lung, it is wholly improbable that the exposure of the general population to this dust is comparable to the intensive exposure to oil which occurs in the mule room." (page 263-265 of ref. 3632)

Although the Kennaways were critical of the role of tarring of roads, their comments were not applicable to other form of coal tar of which there were at least six entities. Kennaway and his colleague reported on chemical and

biologic effects of tar and their overall conclusion was that polycyclic aromatic hydrocarbons caused lung cancer in mice (see below, under European Research on Experimental Carcinogenesis).

Tabulated results and opinions on occupational and environmental factors. The literature of the 1930's can be grouped to the following categories: Group (a) Health hazards of occupational/environmental factors with no mention of tobacco smoking (11 publications); Group (b) Health hazards of occupational/environmental factors with tobacco smoking mentioned and no indications of preferential cause (6 publications); Group (c) Question health hazards of occupational/environmental factors with no mention of tobacco smoking (9 publications); Group (d) Question health hazards of occupational/environmental factors with mention of tobacco smoking (8 publications). The grouping is based on whether the authors favored, questioned, or simply mentioned, occupational/environmental factors separately from tobacco smoking.

Group (a) Health hazards of occupational/environmental factors with no mention of tobacco smoking.

Authors Geographic Location	Results and Comments
(3019) Miller & Jones New York	There were 32 case reports, more than half, laborers exposed to dust, paint and combustion emissions. "From this brief review it is evident that we have a considerable number of theories as to the causation of pulmonary carcinoma which have very little basis of proved fact. We are inclined to agree with authors such as Katz (2731) that the metaplasia caused by such coexisting diseases as influenza, pneumonia or tuberculosis is only one factor, and that there probably are other factors as yet unknown, of which possibly mechanical irritation, such as dust, may be a contributing factor." (page 6)

(3027) Hodge Canada	"It is generally agreed that malignant disease of the lung is increasing. Various causes have been suggested for this increase. It has been thought, for instance, that the irritation of gasoline fumes and the inhalation of particles of tar may play a part." (page 60).
(3232) Kirklin Minnesota	A discussion of Kirklin's presentation by James T. Case of Chicago: "One cannot close this discussion without wondering if the author has anything new to present concerning the cause of the increased frequency of carcinoma of the lungs. I recall that in a recent discussion on this subject the idea was advanced that roads plus the increased use of the automobile resulting in more inhalation of tar products in dust might be one of the causes of the increase in the frequency of carcinoma of the lung." (page 99)
(3328) Gutteridge Australia	"Whether the tar-paving of roads has had any effect is problematical, but it is noted that the increased incidence of the disease in Australia is as belated as has been the conversion of water-bound macadamized roads to tar paving. It is also noteworthy that Iceland, being a hilly forest country, has very few roads or bridges, and the chief mode of transport is by pack-horse." (page 18)
(3420) Churchill Massachusetts	"Various causes have been invoked, among them inhalation of tar dust from the roads." (page 279)
(3417) Geschickter & Denison Maryland	60 case reports analyzed. "Radioactive substances, heavy oils and tar, and chronic inflammatory diseases of the lung are believed to be predisposing factors. The etiological significance of these agents, however, is not well established. Chimney sweeps, aniline and paraffin workers, and miners working with radioactive minerals have been known to develop the disease twenty or thirty years after exposure. The most conclusive series of cases from an etiological point of view are those reported among the miners of Schneeberg and Jachymov after long contact with radioactive ores." (page 857)
(3412) Bronfin Colorado	6 case reports. "Among several causes, Stivelman (2814) mentions the gasoline age and its production of deleterious gases." (page 193)

(3621) Rosedale & McKay New York	"From a knowledge of local conditions it was estimated that 43 patients, or 75.4 per cent of the total number, were emloyed in occupations requiring exposure to dust or other irritating atmospheric factors. We feel that this may possibly be an etiologic factor in producing chronic irritation of the bronchial epithelium, resulting in protoplasia and metaplasia." (page 495)
(3736) Kenning Michigan	"The association of benzine products, such as asphalt, tar and motor gases has been noted. These factors may have some bearing on the relative increase of carcinoma of the lung. x x x Approximately 50% of our own cases were found in people of Polish and Slavic descent." (page 466)
(3918) Jenkinson & Hunter	Discussion of experimental carcinogenesis using tar. "The etiologic factors in bronchiogenic carcinoma as in carcinoma elsewhere, remain obscure. Chronic inflammatory process, inhalation of irritating substances and hereditary susceptibility are all invoked because of their possible contributory importance." (page 2392).
(3951) Lipowitz Canada	"The study of etiology of cancer thus comprises three distinct phases: intrinsic factor that causes tissue injury, an intrinsic factor which is the general susceptibility of the individual, and the transformation of the cell to a malignant status. Möller (2423) painted the backs of young rats with tar and did not produce carcinoma of the skin, but rather carcinoma of the lungs. Similar results were obtained with mice. It was believed that tar acts as a factor in lowering the resistance of mice, while the cancer is caused by the inhalation of irritants. The irritation in this case was due to the fact that the mice lived in burrows under sawdust and hay. Today, the irritation theory of Virchow is regarded as an essential factor in the aetiology of carcinoma of the lung." (page 10)
(3952) Anonymous AMA foreign correspondent in France	"For years a recrudesence of primary pulmonary cancer has been observed in France. Kling, Samsonov and Heros think that one of the causes of this increase is the tarring of roads. Statistics offer little to confirm the responsibility of tar. Kling and his collaborators do not propose to proscribe tarring but they would like to see employed only innocuous substances. Benzopyrine contained

within the tar used nowadays has a high cancerigenic effect on animals, inducing cancers of the epidermal epithelioma type. Benzopyrine can be mixed accurately with tar. Its proportion is about 0.5 per cent. Since from 2 to 3 Kg. of tar is spread over a square meter, one can gage the amount of benzopyrine used. Benzopyrine adheres solidly to particles of silica and other materials spread over roads. The benzopyrine-impregnated dust raised by the wind can be borne a great distance from its source and carry with it the harmful tar. A certain number of substitutes for tar in use at present for the coating of roads, such as natural pitch and petroleum resin, do not cause cancer in animals." (page 245)

Group (b) Health hazards of occupational/environmental factors with tobacco smoking mentioned and no indications of preferential cause.

Authors Geographic Location	Results and Comments
(2931) Lickint Germany	"As generally known, in the search for the cause of this phenomenon, a number of causes have been considered (better diagnoses, frequent occurrence of influenza, automobile combustion, gas, street dust, road tar, war gas and others." (page 10 of English translation)
(3011) Bonner Georgia	"Chronic irritation may be considered one of the principal factors in the production of lung cancer. Some have believed the dusty air, the presence of gases from automobiles, the use of tobacco and the inhalation of particles of tar from the road beds to be possible etiologic factors. Konrad and Franke state that in Riga there has been a definite increase but that there has not been a coincident increase of automobiles and the use of tar in road building. Thus these factors could not account for the increase of lung cancer in this locality." (page 1045)
(3327) Pilcher & Brindley Texas	"Increase of tar in the air from roads, gas fumes from automobiles and industrial plants, and irritating stone dusts have all been discussed as possible factors in the increasing incidence of the condition. These ideas were furthered when Kimura (2321), reported the experimental pro-

duction of pulmonary cancer in animals by the intratracheal insufflation of the lungs with coal tar. The great incidence of the condition among the cobalt miners in Schneeberg, Saxony, is proverbial. Increased smoking of tobacco has been mentioned also. None of these things have been proved to be significant. In our series it is interesting to note that five of the eight men patients were heavy smokers of cigarettes, although this may not be greater than any unselected group of men. We also note that of this group two had been for a long time restaurant cooks and one a baker. Another dated his symptoms from his work in an oil field, where he was exposed to fumes which were quite irritating to him. Two others had a history of chronic cough off and on for as long as they could remember. These findings, while suggestive, are not presented as proven etiological points in these cases." (pages 248-249)

(3645) Schrire
South Africa

"The etiology of carcinoma of the lung is obscure; attempts to produce it experimentally having up to the present failed. Some writers have tried to explain the recent increase in the recorded numbers by blaming petrol fumes, tarred roads, oil fumes and tobacco. The condition, however, is probably as common in South Africa as anywhere else in the world, and one has seen cases in people who have never been in a motor-car and who saw tarred roads for the first time on arriving at the Somerset Hospital for investigation." (page 475)

(3833) Faget & Harmos
Virginia

"Among the predisposing etiological factors various inflammatory lung diseases, such as influenza, bronchitis, bronchiectiasis and tuberculosis have been listed. Chronic irritation from the inhalation of smoke and dust has also been blamed. Arkin and Wagner (3613) found 90 percent of their patients were chronic smokers. All of our patients were heavy smokers. Jaffe believes syphilis, by causing a chronic irritation of the bronchial mucosa, may be of importance in the pathogenesis of lung cancer. Syphilis was present in 24 per cent of his cases. The inhalation of automobile exhaust gases and the emanations from tar on roads are other agents advanced to explain the growing incidence of pulmonary malignancies". (pages 22-23)

(3929) Hochberg & Lederer New York	"Numerous theories have been advanced as to the bearing of inhalation of dusts or of tar from roads as a possible etiologic factor in carcinoma of the lung. No evidence of any such connection has ever been proved. Nor have tuberculosis, influenza, tobacco and war gases been shown to be etiologic agents. x x x. Kennaway and Kennaway (3632) have shown that the factors which lead to silicosis appear not be active in the production of cancer of the lung. They also have shown that in certain open air occupations in which there is exposure to the dusts of the road, the percentage of cases of carcinoma of the lung was high, whereas drivers of motorcars had a normal incidence. In this study they also showed that workers exposed to coal gas and tar tend to have a higher incidence of cancer of the lung." (pages 81, 82)

Group (c) Question health hazards of occupational/environmental factors with no mention of tobacco smoking.

Authors Gegraphic Location	Results and Comments
(3026) Boyd Canada	"The literature contains suggestions as to countless etiological factors. Of these only three need be mentioned - tuberclosis, influenza and the inhalation of irritating subtances. The first two have played no part in my own material. Regarding the third it is more difficult to be quite so definite, for the variety of possible irritants is great. It has been pointed out by numerous writers that the recent increase in the incidence of carcinoma of the lung coincides with the enormous increase in automobile traffic, the inference being that the inhalation of exhaust gases stimulates the bronchial mucosa to malignant growth. The widespread tarring of roads has been similarly blamed. In Western Canada there are no tarred roads, and most of the patients come from country districts where the contamination of the air by exhaust gases is negligible. I have never seen a case in a garage worker, although such a man is continually exposed to the waste products of gasoline in concentrated form." (page 240)
(3037) Maxwell & Nicholson Great Britain	"In the present series of London cases sixty-six were engaged in indoor and thirty-four in outdoor occupations. It must be remembered that a

hospital in a large city draws its patients from a considerable part of the surrounding country, and the proportion of indoor to outdoor workers will vary with the proportion of city to country dwellers admitted. Also, we cannot be sure as to the length of time for which the occupation stated in the clincial notes had been followed, and we have to accept these statements at their face value; changes in occupation, recent or old, are not as a rule reflected in the notes, so that the classification is open to a very serious fallacy. Again, in many cases it is not easy to generalize as to the precise nature of some occupations on the lines of this classification, and such cases weaken the value of these figures. After careful consideration we have reached the conclusion that from our own figures, at least, there is no evidence to suggest that the outdoor worker is more liable to contract a bronchial carcinoma than his indoor colleague, and that the assumption of some atmospheric impurity to explain the increase in incidence of the condition is not justified by the evidence.

It must also be remembered that nearly the whole population spends so much of their leisure time nowadays in the open air that such possible aetiological factors as tar and road dust and fumes of oil and petrol are likely to be of almost equal importance in all irrespective of their occupation.

With regard to specific occupations, there was none which occurred with marked frequency in this series, nor post mortem was any occupational lesion found which might have been held to account, even in part, for the presence of the growth." (pages 21-22)

(3121) Peet
Great Britain

"Much also has been made of the inhalation of tar emanations as a possible aetiological factor, and although there has been an increase in the practice of tarring roads, there is insufficient evidence to justify correlating this fact with the increased incidence; nor has any association been found between the disease and tar workers. Ewing's (1919) dictum that in pulmonary carcinoma: 'The chief aetiological factor is pulmonary tuberculosis,' has not been confirmed by this study. In none of the cases was there evidence of pulmonary tuberculosis of an extent and character such as could be related to the carcinoma." (page 106)

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(3438) Sears Great Britain	"Exhaustive studies of the occupational incidence have been made, and, although the labouring classes appear to be most often affected, no occupation was found predominant. Many irritants such as road dust, tar and exhaust fumes have been suggested to account for the statement made by some observers that the disease is more common in outdoor workers, but as yet no definite conclusions have been reached, and the aetiology is as obscure as that of cancer in general. It can be said, however, that infection and other types of irritation do produce epithelial metaplasia which is suitable soil for the development of cancer." (page 106)
(3433) Edwards Great Britain	"As far as can be determined at present, occupation does not appear to be of any etiologic importance; and, although the previous history often contains evidence of influenza, bronchitis and pleurisy, it is more than probable that these are the first signs of the malignant changes in the lung rather than actual predisposing factors." (page 108)
(3530) Andrus New York	"A survey of the occupations of these patients yields nothing which might in any way be considered as of etiologic significance. Eighty per cent did inside work or desk work, while 20 per cent worked out of doors; of the latter there was one stonecutter, four were 'laborers,' three were farmers, one a gardener, and one a bricklayer." (page 236)
(3626) Rice Wisconsin	"The occupations of these patients also appeared to be of little significance. The distribution of indoor and outdoor work was similar to that of the hospital admissions as a whole and the number engaged in occupations with special hazards was no greater than for the unselected cases." (page 907)
(3815) Stein & Joslin Illinois	"Although an exhaustive study was made of the various occupations in this group, no conclusions of any significance could be drawn. At least 75 different occupations were represented, the largest group being farmers or common laborers. Eight, or 5 per cent, of the patients had been coal miners but 4 of these also had been employed

in other occupations. In addition there were 2 patients whose occupations conceivably might have had some bearing upon the disease. One patient had worked originally as an ore miner, later as a metal plisher and motor assembler. A second patient had been employed for 7 years as an emery polisher inhaling fine particles of emery dust.

Rosedale and McKay (3621) state that 75.4 per cent of the patients listed in their group of 57 were employed in occupations requiring exposure to dust or other irritating atmospheric factors. It is difficult to evaluate properly the part that dust and irritative atmospheric factors play in the etiology of carcinoma of the lung, especially in patients coming from large cities or industrial centers. There have been no conclusive facts shown as yet to prove that the above are of major importance." (page 904)

(3812) Boyd
Canada

"These are nearly all based on the supposition that some carcinogenic agent is inhaled from the air, some agent which we owe to recent industrial and scientific advances. The favorite culprit is tarring of roads, an idea supported by the indisputed facts that tar when applied to the skin may produce carcinoma, and that inhalation of tar dust may produce cancer of the bronchial tree in the experimental animal. This is as reasonable as to say that cancer of the skin in man is usually caused by tar, or that the ingestion or inhalation of aniline dyes is the common cause of carcinoma of the bladder.

The material on which this paper is based represents a cross section of the city of Winnipeg and the province of Manitoba, a part of the country where tarred roads are remarkable for their absence. Nor can the inhalation of automobile waste products be a factor of importance in the great open spaces of the Western prairie. The disease is common in Russia where there is no tarring of roads and few automobiles. Dr. E. L. Turner, who spent ten years at Beyrut, Syria, assures me that cancer of the lung is as common there as in Philadelphia, yet most of his patients lived under the same conditions as did their forefathers in the days of the Pharaohs." (page 318)

Group (d) Question health hazards of occupational/ environmental factors with mention of tobacco smoking.

Authors Gegraphic Location	Results and Comments
(3003) Davidson Great Britain	"Tobacco, war gas, petrol fumes, dust, and tar from the roads have all been subject to discussion as possible and likely sources of irritation, but it cannot be said that any observations have been made so far which justify definite conclusions as to the aetiological importance of these factors, and such control evidence as there is does not lend much support to the theories in its favour. The Brompton Hospital records do not add anything material to the facts furnished by the above investigations. Of the 107 cases, confirmed by autopsy, the occupational incidence was as follows: Housework (including married women, unmarried housekeepers and domestic servants), 11; labourers, 9; painters, 4; porters, 6; clerical work (L.C.C. clerks, civil servants, post-office clerks), 11; policemen, 2; travellers, 3; motor drivers, 2; chauffeur, 1; engine driver, 1; steam-wagon driver, 1; carman, 1; not recorded, 9. This makes a total of 61. The remaining 46 comprise all sorts of artisans and workers in different shops, stores, etc., railway officials other than porters, and various occupations not included under the above descriptions. After deducting from the total number the 9 cases where occupations were not recorded, the remaining 98 were divided into indoor and outdoor workers respectively, so far as it was possible to differentiate these, having regard to the fact that some of the occupations specified included workers in both classes, with the result that equal numbers were found (49 of each). Deducting the 18 females from the indoor workers, we have 31 indoor occupations to 49 outdoor occupations among the male cases. From this it can hardly be suggested that any special conclusion can be drawn as regards indoor and outdoor occupations in relation to the disease in question." (pages 34, 36-37)
(3222) Brockbank Great Britain	"An investigation of the occupations of 898 cases of primary lung cancer collected from the literature suggests that the labouring classes predominate, although no one occupation stands out. Poison war gas, tobacco smoking, road dust, and motor-car fumes are all possible aetiological

factors. The occupations of sixty-two cases have been investigated in some detail. Nine (14.5 per cent.) seemed to have definitely dusty jobs, and eighteen (29 per cent.) worked amongst gases and fumes. Four were badly gassed in the war, and nine smoked excessively." (page 37)

(3212) Rogers
Austria

"A study of environment or occupation proved of little significance. The patients were all born either in Austria or in one of the adjacent countries, and were all from the working class. The number of years spent in large or small communities, factory centers, farming districts, etc., was not obtainable from the existing records. The occupations were varied, and were thirty in number. In only one patients was a history of a chronic cough as a result of his occupation noted. This patient was an upholsterer. The largest number in any one occupation was among the women, 6 being domestic servants. Of the 39 men only 5 could be said to have been subjected to more than the average amount of respiratory irritation, as far as their stated occupations were concerned. Irritating fumes of any sort, with the possible exception of tobacco, did not seem to play a role." (pages 1058-1059)

(3627) Fleckseder
Germany

"The profession of our patients does not seem to have had a significant influence on the development of BrCa. For painters, vascular damage caused by lead, for waiters and coffee makers, the harmful effect of tobacco smoke could play a role. The relatively large ratio of outdoor professions is somewhat noticeable and can possibly be attributed to the more frequent occurrence of different lung diseases in these profession." (page 4 of English translation)

(3603) Craver
New York

"Claims have been made, both for and against the etiological role of tobacco smoking in cancer of the lung. In 48 male patients with cancer of the lung who gave a statement about their use of tobacco, 31 or 64 per cent were classed as having smoked to excess. In 10 instances this history of heavy smoking was associated with the factor of an occupation that was probably irritating, in 3 instances with a history of repeated or severe respiratory infections, and in 4 instances with both an occupational factor and a history of respiratory infections. On the whole, these figures do not seem very impressive, and seem almost to

	call for the assumption of some additional factor of special susceptibility of the bronchi to forms of irritation that are probably present to an almost equal degree in subjects who do not develop cancer of the lung." (page 351)
(3724) Husted & Biilmann Denmark	"With regard to the significance of the noxious influence of some particular occupations, the present material offers absolutely no suggestion of that kind. These patients, eight women and 27 men, came from all classes of society and represented a quite accidental mixture of all occupations, without predominant frequency of any occupation or group of workers. It is quite true that no mining is done in this country, but apart from one patient who was a stoker the material contains no cases in which it would be reasonable to assume that the patient had been exposed to the effect of dust and smoke more than all other persons in general. In this connection it is also to be mentioned that any marked degree of anthracosis of the lungs was found in two cases only. Tobacco has frequently been discussed as an etiological factor, but our patient material includes no tobacco workers, and according to the case records only four of the patients were particularly heavy smokers." (page 351)
(3705) Frissell & Knox New York	"In our series of cases occupation did not play a significant part. There were no miners in the series and only 3 were engaged in dusty trades - a bricklayer, baker, and fireman. Neither were the habits of the patients of significance, except for the well-nigh universal use of tobacco. One had been a victim of war gas. Ten of the cases were in females, 36 in males." (page 223)
(3855) Frank Colorado	"Chromates and tobacco smoke have also been implicated. Carcinogenic agents have been studied extensively. 'For many years it has been known that a variety of agents are capable of inciting malignancy (Andervont). Among these are the sex hormone estrin, benzopyrene, an azo-compound (o-amido-azo-tuluol) and 1.2,5,6-dibenzanthracene. Since 1930, approximately forty-five definite chemical compounds have been discovered which are capable of eliciting tumors in experimental animals. Up to the present, there is no possibility of arriving at any generalization regarding molecular structure necessary for cancer inciting properties. The only property common to the

> various compounds is the presence of at least two benzene rings. It has been found that the lungs of one particular strain of mice are delicate test objects for the carcinogenic activity of 1,2,5,6-dibenzanthracene; for, in so far as macroscopic evidence is concerned, the pulmonary tumors appeared earlier than those arising at the site of subcutaneous injection. The fact that tumors appear in the lungs of some mice following the subcutaneous injection of 1,2,5,6-dibenzanthracene may be of interest, for it suggest that inhalation of carcinogenic agents may not be essential for the development of some pulmonary tumors of other species.
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> According to the Kennaways (3632), workers exposed to coal gas and tar, and those engaged in the preparation and sale of tobacco, tend to show an increased prevalence of cancer of the lung. Occupations concerned with the supply of alcohol have a high incidence of cancer of the larynx. No evidence has been found that tarring of roads has affected the incidence of cancer of the lung in the general population. Such data as are available suggest that coal tar in the atmosphere from any source does not readily give rise to this condition." (page 469)

The above list does not identify the sepcialty of authors but this can be derived by re-examining the articles. It may prove enlightening to determine the specialty of authors who question environmental/occupational factors and do not mention tobacco smoking. Boyd, a Canadian pathologist who wrote a textbook on human pathology, also wrote two articles eight years apart (3026, 3812). He, and possibly other contemporaries, appeared to have favored intrinsic or hostal predisposition factors, and questioned the importance of extrinsic factors, environmental/occupational, as well as tobacco smoking.

Lung cancer deaths in Sheffield tradesmen. Turner and Grace analyzed twelve occupational groups of males in Sheffield, England, from 1926 to 1935 inclusive. Lung cancer comprised 9.6 per cent of 3861 cancer deaths. The

following groups showed significantly greater lung cancer mortality: foundry workers and smiths, grinders, engineers and transport workers; compared to mortality experience by clerks, business and professional men (3811). These observations confirm essentially those of Duguid (2721) and the Kennaways (3632).

Lung cancer deaths in U.S. veterans. Nolan reviewed 1250 autopsy records of the Veterans Administration from 1921 to 1932. Lung cancer deaths were 0.88 percent of all autopsies, and 9.2 percent of all cancer deaths (3211). Matz reviewed records up to 1937 and noted that lung cancer deaths were increased to 2.4 percent of all autopsies in 1932, and 5.3 percent in 1937 (3856). Of the 138 lung cancer patients, 36 percent gave a history of being connected with occupations or industries in which there was a possibility of irritation and traumatization of the respiratory tract. The fact that so large a percentage had been engaged in occupations which caused respiratory tract irritation was supportive of occupational etiology of lung cancer.

Japanese Research on Experimental Carcinogenesis.

The positive results reported from Japan were cited by Harris as to why American tobacco companies should have conducted research on lung cancer. Before Pearl Harbor, Japanese scientists published through Nipponese medical journals that were rarely read by Americans. For the benefit of Westerners, important medical developments were contributed to German journals and occasionally in American or British publications. In 1937, Kinoshita summarized the studies on 'cancerigenic' chemical substance conducted by

Japanese investigators. The chronology of events derived from Kinoshita's review and other sources was as follows:

1905 Yamagiwa proposed that "repetition or continuation of chronic irritation may cause a precancerous alteration in epithelium previously normal." (see ref. 1814)
1914-1918 Yamagiwa & Ichikawa confirmed Yamagiwa's hypothesis by painting coal tar on rabbit ears for 70 to 150 days resulting in metastasizing epithelioma (1513, 1814).
1923 Kimura reported adenocarcinoma in guinea pig lung following intra-bronchial insufflation of coal tar (2321).
1930 Arai & Kikitsu reported lung cancer cases but no information on smoking habits (3038).
1931 Chikamatsu tested tobacco tar in rabbits and mice (3129).
1932 Yoshida reported hepatic cancer in rat following oral administration of o-aminoazotoluene (Cited in 3711).
1937 Taki tested substance isolated from tobacco tar (3737).
1937 Kuroda reported coal-generator gas workers developed lung cancer (3738).
1937 Kinoshita reported hepatic cancer in rat following oral administration of butter yellow or N-methylated compound of o-aminoazotoluene (3711).

I personally would have doubted the credibility of Kinoshita's report if his article was read after Japan occupied China and Southeast Asia (see pp 47, 48 above). Taki "collected tobacco tar from Japanese tobacco pipe which was first dissolved in ether and filtered, and then this ether solution, after shaken with hydrochloric acid and repeated with water to eliminate pyridin, nicotine, etc., was separated and condensed by evaporation. The product was applied twice weekly to the skin of mice. During the experiment the number of animals was increased on several occasions, until the total number was 104.0 of this number, 94 died in 100 days or less. Out of the surviving 10, five have already passed the 130 day mark, two of which shows cancers and the other three papillomas. In one case the first papilloma was noticed after 85 days." This is Kinoshita's description of Taki's experiment that was subsequently published in Japanese (3737); an English translation has become available. Kinoshita has characterized Taki's results as indicating that "tobacco tar" showed

"high carcinogenic potency" but he did not mention any reference compound for comparison. A Japanese scientist is needed to translate the articles published prior to, and after 1937. There are reports on experimental carcinogens such as: constituents of coal tar, constituents of tobacco tar, hormones, cholesterol, sugar-tar, and pityrol (tar residue formed during polishing of rice). The available information suggested that Japanese scientists by 1937 suspected coal tar as a pulmonary carcinogen based on animal experiments and lung cancer among coal gas workers. As to smoking and lung cancer, I could not find articles by Japanese on smoking habits of lung cancer patients. Arai and Kikitsu reviewed 4,663 autopsy records from "34th year of Meiji or 1901, to the 15th year of Taisho or 1926", or starting a quarter century before the ascendency of the late Emperor Hirohito. Lung cancer in Japanese was 2.6 percent of all cancer cases, whereas European figures during the same period exceeded 10 percent. Arai and Kikitsu reported that there was one case associated with external injuries to the chest, two followed influenza, and three were employed in dusty occupation (3038). There was no mention of smoking habits. The authors cited European publications relating to dust inhalation and lung cancer i.e. Hampeln (2328), Schmorl (2329), and Uhlig.

European Research on Experimental Carcinogenesis.

The animal experiments needed to support the coal tar hypothesis were conducted at research laboratories in Europe. There were six laboratories in Great Britain, one in Scandinavia and another one in France. During the 1930's, the Germans were no longer active in animal coal tar experiments and instead directed their interest to "tobacco tar". It was rumored that the sale

of tobacco, monopolized by Jewish merchants, had to be discouraged by Nazi physicians, disguised for health reasons (see Chapter IV).

Research Institute of the Royal Cancer Hospital, London. Unlike the Cancer Research Institute headed by Roffo in Argentina, the policy at the London Institute was to have scientists publish under their own names: E.L. Kennaway, I. Hieger, J.W. Cook, C.L. Hewett, G. Barry, G.A. Haslewood, W.F. Mayneord, W.E. Bachmann, A. de Dansi, C.G.M. de Worms and A.M. Robinson. The chronology of their accomplishments was as follows:

(2415) Kennaway	Reviewed literature on chemistry of seven forms of tar reported to produce skin cancer in workers.
(2416) Kennaway	Isoprene heated 720 to 920 C.
(2517) Kennaway	Yeast, human skin, Durnham coal, California petroluem, isoprene and acetylene heated 720 to 929 C.
(2524) Kennaway	Anatomical distribution of occupational cancer.
(2825) Kennaway & Sampson	Cholesterol heated.
(3039) Kennaway	Aluminum chloride added to tetralin, acetylene, xylene, naphthalene, bromobenzene and tetrahydro-naphthalene, pure synthetic 1:2:7:8-dibenz-anthracene.
(3040) Kennaway & Hieger	Fluorescence spectra bands at 4000, 4180 and 440 Au. for most carcinogenic materials.
(3233) Cook, Hieger, Kennaway & Mayneord	Test for skin-cancer producing action on mice for polycyclic aromatic hydrocarbons including dibenz-antracene.
(3333) Cook, Hewett & Hieger	Isolated and synthesized skin-cancer producing hydrocarbons from coal tar including benzpyrene.
(3544) Barry, Cook, Haslewood, Hewett, Hieger & Kennaway	Isolation of tetracyclic and pentacyclic hydro-carbons from coal tar.
(3739) Hieger	Fluorescence spectrum of 3,4-benzpyrene.

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(3740) Bachmann, Cook, Dansi, de Worms, Haselwood, Hewitt & Robinson	Derivatives of methylcholanthrene, benzanthracene, benzpyrene and benzphenanthrene.
(3741) Cook, Haslewood, Hewett, Hieger, Kennaway & Mayneord	Review chemistry and experimental carcinogenicity of polycyclic aromatic hydrocarbons.

I have rated the above record of accomplishments as the most outstanding for the 1920's and 1930's. It should be noted that Harris used three of the 13 above articles and concealed the purpose and outcome of the studies. The overall purpose of Kennaway and his collaborators was to develop chemical (fluorescence) and biologic (mouse skin painting) tests for identification of carcinogenic compounds in coal tar. They were able to identify the most active cancer-producing compounds yet encountered as belonging to the cholantherene group and were of special interest on account of their structural relationship to bile acids. The carcinogenic properties of 3,4-benzpyrene, a constituent of coal tar, and 1.2-benzanthracene derivatives were described. However, the group lamented that "little progress has been made in elucidating the mechanisms of cancer production by chemical compounds," although they enumerated a number of genetic and other factors that influenced carcinogenesis such as hormones, diet and radiation.

> "The results obtained in the last few years have shown that a variety of tumours, as carcinoma of the skin, kidney, testis, bladder, liver, and uterus and sarcoma of the subcutaneous tissue, peritoneum and spleen, can be induced by pure chemical compounds and doubtless many of the negative instances collected under heading VI, p. 235, will be eliminated by the use, either of known compounds in other media, or of compounds not yet tested, or not yet synthesised. All these results indicate that the variety of tumours which occur naturally in different organs, and in different species, might be due to the production under conditions of disease of a variety of carcinogenic chemical compounds. But the mere fact that one can imitate a natural process by the use of an artificial agent does not of course prove that one has discovered

the actual agent by which the natural process is brought about. Thus, many compounds will produce oestrus, and it is certain that some of them at least are not the causes of natural oestrus. Again, calciferol is antirachitic, but there is now evidence that it is not the antirachitic substance occurring normally in animals. Hence, the line of investigation that now requires to be followed in cancer research is not so much the production of tumours by artificial means as, what is incomparably more difficult, the discovery of the actual factors by which the naturally occurring tumours are induced.

The high incidence of experimental cancers induced by many workers in different parts of the world in an appropriate tissue and species under the influence of one of the more active carcinogenic compounds, as benzpyrene or methylcholanthrene, suggests that the introduction of some extraneous factor is not essential for the onset of cancer, although one would not deny that such factors may exist, and may give rise to some forms of cancer.

The increase in the frequency of a naturally occurring form of cancer, as, for example the occurrence of cancer of the lung in 20 per cent instead of in 5 per cent of mice, in the presence of a known carcinogenic agent suggests that this agent can summate with the unknown, naturally occurring carcinogenic factor to give an effective stimulus. Burrows has evidence (in course of publication) that in the rabbit the incidence of cancer of the uterus can be affected in the same way. This summation of causative factors suggests very interesting possibilities in the study of cancer.

Investigation of the chemical carcinogenic agents, which were the outcome of studies of industrial cancer, has been carried a stage nearer the realm of normal biological phenomena by the demonstration of a structural relationship between certain of these compounds and normal constituents of the human body. The laboratory transformation of bile acids into methylcholanthrene suggests the possibility of such changes occurring in the body, and doubtless many workers will consider such possibilities in connection with future investigations concerning the formation and degradation of cholesterol in the animal organism.

Attention has been directed already to our ignorance of the mode of action of the chemical carcinogenic compounds in producing cancer. Obviously it is desirable that investigation of the problem should be pursued, both from the point of view of obtaining a better understanding of the nature of the malignant change, and also in connection with the search for therapeutic agents against cancer. The use of pure chemical carcinogenic compounds should materially assist such studies on account of the certainty with which malignant tumours may be induced by these agents under exactly defined and reproducible conditions." (pages 242-243 of ref. 3741)

The summation theory was not pursued by Campbell but will be discussed further when environmental carcinogens are individually reviewed (Part Four).

National Institute for Medical Research at Hampstead. Harris quoted two of ten publications by J. Argyl Campbell on the subject of experimental carcinogenesis in mice. The pertinent publications were as follows:

(3636) Campbell "It is shown that carbon monoxide breathed for prolonged periods (one-third of life) retards, but does not prevent, development of tar cancer in mice. There is no evidence herein in favour of the hypothesis that the recently reported increase in human cancer is connected with the presence of carbon monoxide in the air of streets, garages, factories, kitchens, etc. Breathing oxygen at 60 per cent. of an atmosphere has no effect upon development of tar cancer in mice." (page 245)

(3453) Campbell "Mice were repeatedly exposed to dust obtained by sweepings from tarred roads and containing about 2 p.c. of tar. Cancer of the skin developed in 70 p.c. of those surviving long enough. The incidence of primary adenoma of the lung was increased to tenfold that of the controls: the lungs of the dusted mice contained much dust. The breathing of carbon monoxide, if anything, retarded the effects of dusting.

The bearing of this research upon the debated increase in tumours of the human lung cannot be assessed at present. The mice were exposed to much more excessiving dusting than occurs with human individuals. Cleanliness prevents cancer of the skin in man, and the natural mechanism for removal of dusts from the healthy lung may suffice for the small amounts of dust inhaled.

There is the further question whether these tumours of mice may be compared with those of the human lung. The experiment with mice is to be repeated and attempts will be made to transplant some of the tumours; the effects of dust, with the tar products removed, will also be studied." (page 294)

(3642) Campbell "1. Mice were exposed for 7 hours on 5 days each week during most of the lives to exhaust gases from internal combustion engines in concentrations somewhat resembling those obtaining in traffic blocks and garages. There were no marked effects upon the well-being of the mice. Carbon (soot) and lead were excluded in these experiments.

2. Mice were similarly exposed to fumes and tarry matter from cigarette smoke without any marked pathological effects.

3. The incidence of primary lung tumours in mice is considered in detail. These tumours are usually rare before

the latter half of the second year of life. Exposure to exhaust gases has little effect upon this incidence when compared with the controls. The incidence for the tobacco group of mice is on the high side, but these mice survived longer than the other groups.

4. The incidence is increased by dust collected from tarred roads, as shown previously. Some of these tumours are definitely malignant in appearance. It is not known yet whether the dust freed from tar has any influence; this question is under examination, and the results should be available in a few months. Age and heredity have an influence on the incidence of these primary lung tumours of mice, but these factors are not responsible for the result with the tar dust. This dust contained much more tar than the tobacco smoke." (page 157-158)

(3742) Campbell

"(1) Some evidence has been obtained recently both from human statistics and experiments with mice that road dusts (with and without tar) and other dusts increase the incidence of lung tumors. In mice the increase is higher when the tar is also present in the dust.

(2) Gases and fumes from internal combustion engines under ordinary circumstances do not influence the incidence of lung tumors. Motor vehicles may however play some part by constantly stirring up the fine road dust.

(3) Some statistics indicate that workers with tobacco are liable to cancer of the lung and larynx. Some animal experiments give evidence that tobacco smoke and fumes may cause a slight increase in incidence. Further work is required, but this factor does not appear so important as the road dust.

(4) Animal experiments indicate that heredity may play an important part in susceptibility to lung tumors. The susceptibility may be increased by subcutaneous injection of certain agents. Even here it is suggested that the irritant or stimulus to start the tumor comes from the external environment. Under ordinary conditions this stimulus may be below the threshold.

(5) The earlier work with animals was of too short a duration to obtain undeniable evidence regarding the effects of dust etc. upon the incidence of lung tumors and more experiments of a prolonged nature are required. Lung tumors are late in development.

(6) So far as the evidence goes it supports the 'irritant' theory for cancer of the lung and indicates that there may be several irritants - coming from the external environment - and several factors e.g. heredity capable of exerting an influence.

(7) There is no substantial reason why the results for experiments with mouse lung tumors should not be applied to man." (pages 456-457)

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(3743) Campbell "(1) It was shown previously that dust from tarred roads causes cancer of the skin of mice. Road dust minus tar, as removed by benzene, does not cause cancer of the skin of mice; it stimulates the production of lung-tumours in mice, but not to so great an extent as when the tar is also present. Lung-tumours are rare in mice before they are 12 months of age.

(2) The dust does not cause any obvious inflammatory reaction - apart from the tumours themselves - in the lung or lymph-glands.

(3) Perhaps the presence of lung-tumours amongst some of the control mice is due in part to the dust breathed from the contents of their boxes or from the general atmosphere. This dust may contain a carcinogenic agent, e.g. tar, or it may 'irritate' the lung without obvious inflammatory reaction.

(4) Tar, either by a direct action on the lung itself or indirectly by some action on other tissues, or both, stimulates the production of lung-tumours in mice and hastens their appearance.

(5) Metastases from lung-tumours in mice are recorded, for the first time in this country, so far as we know. The majority of the lung-tumours in the dusted mice are malignant." (page 223)

(3857) Campbell "Sir, - With reference to the recent annotation (Br Med J March 26, p. 682) on the subject, some further information may be of interest. In some respects it is possible to bring the Joachimstal (and presumably Schneeberg) miners' lung cancers into line with those observed in metal grinders and in the mice exposed to road dust. In all cases, besides silica in some form, iron is present in the dust. Some of the inorganic contents of the Joachimstal dust resemble very closely those of the road dust, which produce lung cancer in mice. The presence of some form of iron and silica in these dusts is suggestive, and further experimental work is in hand dealing with this aspect of the problem." (page 955)

(3953) Campbell "(1) Tarry matters from the following have been tested for carcinogenic potency, using the mouse-skin test: Dusts from tarred roads; cigarette smoke; chimney soot; soot from exhausts of internal combustion engines burning heavy oil; a binding material in cardboard.

(2) As proved by the production of skin cancer, the tarry matter from tarred roads contains potent carcinogenic agents as does chimney soot, but under ordinary conditions the effect of the latter in its action on the skin seems to be mitigated somewhat by the presence of the carbon of the soot, while the effect of the former seems to be aided by the presence of inorganic constituents.

(3) Cigarette smoke, under ordinary circumstances, gives rise to tarry matter which may occasionally produce hyperplasia and cancer of the skin after prolonged application.

(4) Tarry matters from the motor-exhaust soot and from the cardboard tested do not produce cancer when painted on the skin of mice.

(5) Exhaust soot suspended in the atmosphere slightly increases the incidence of lung tumours in mice, while chimney soot does not produce any noticable increase. The dust from tarred roads appears to be the most dangerous source of carcinogenic agents; when inhaled it gives the highest incidence of lung tumours in mice. It is considered that here again the inorganic constituents in this dust (for example, silica, iron) enhance or aid the effect of the tar, while, on the other hand, the carbon of soot tends to mitigate any effects of the tar present in producing tumours of the lungs. Irritation without inflammation appears to play a part in genesis of these tumours both in control and experimental mice.

(6) Although some primary lung tumours in mice are simple adenomata, other tumours reveal characters of typical malignancy with production sometimes of metastases. Further examples of metastases have been obtained." (page 131)

(3954) Campbell [Response to annotation in Lancet, see below]

Harris misunderstood Campbell's interpretation of the experimental results, probably because he examined only two publications (3642, 3953). Even the two he selected did not specifically state that cigarette smoke was a cause of lung cancer. A reading of an annotation in Lancet would have avoided the confusion (3643).

"In the present experiment the mice, on the per kilo basis, were exposed to conditions resembling at least those of a more than moderate cigarette smoker. Nevetheless there was no effect of any importance upon death-rate, body-weight and rate of growth of mice. There were 17 experimental mice and 11 control mice with primary tumours of the lung; the increase in the case of the former will be discussed later. Three of the experimental females showed mammary carcinomas. The other pathological changes resemble those given for the mice in Exp. A and are of no obvious significance. Fertility was tested, and there was no change compared with the controls.

Although suggestive, we do not consider that the incidence of lung tumours in the cigarette smoke experiment is high enough above that for the controls of the same age - 919 days - to demand special attention, because the increase is due to mice which

survived longer than those of any of the other groups (pages 154-156 of ref. 3642)

The second paper quoted by Harris contained the following paragraph, reiterating that lung tumors appearing after skin painting were related to spontaneous appearance because of aging:

> "'Tar' from cigarette smoke. - Cigarettes were smoked artificially (Campbell, 1936) and the hot smoke was passed through a cool glass tube, in a side bulb of which some of the substance of the smoke condensed to form a dark brown liquid. This was concentrated and painted on the skin of 23 mice in the usual way, twice a week for 20 months. In one case a typical epithelioma developed, the wart being first noticed after 16 months of painting. In another of these mice which had been painted for 20 months the painted area of the skin at death was much thickened, and on section revealed the typical hyperplasia, which represents the first stage of cancer reaction to tar painting. The tarry matter used had not been exposed to a temperature higher than that produced in cigarette smoked in the ordinary way. Compared with the road tar this tobacco 'tar' is certainly not very active, but it apparently may give rise to cancer of the skin after prolonged application.
>
> Seven, or 35 percent., of the 20 mice living 10 months or longer and painted with cigarette 'tar' exhibited primary carcinoma of the lung. Twelve of these mice lived for 2 years or longer - that is, to an age favourable to the development of lung tumours." (p 126, ref. 3953)

Campbell took the opportunity in response to the annotation in Lancet, to justify the use of mice in the investigation of pulmonary carcinogenesis:

> "Sir. - The annotation on p. 521 of your last issue implies that mice are more susceptible than other laboratory animals to spontaneous tumours of the lung. This may be more apparent than real. Other laboratory animals are killed usually early in life, while mice, which live only about two years, are far more frequently allowed to fulfil their allotted span of life. Since tumours of the lung in mice and man are most prevalent during the last quarter of full life, it is probable that the same will hold for other animals. At any rate it has not yet been determined for them one way or the other to my knowledge. Moreover inbreeding in mice is much more common.
>
> Again you state that mice are more susceptible to carcinogenic tar than other animals. This may be due merely to the fact that in tar-painting experiments the painting usually covers only up to six months. This period is about one quarter, or a large

fraction, of a mouse's life, but a much smaller fraction for other laboratory animals. For a fairer comparison tar-painting should be prolonged for a quarter of their full lives also. Further so far as the evidence goes the skin of man is as susceptible to tar as is that of the mouse. This is why I chose mice for my dusting experiments.

Your statement, that the conclusion from my dusting experiments is that the tar in the road dust is responsible for the increase in incidence of lung tumours, needs some adjustment. My paper, mentioned by you, indicates that tar is only one of the factors, since the road dust still causes a definite but smaller increase in incidence of lung tumours when the tar is removed from it. I certainly have not put so much emphasis on the part played by the tar alone. The inorganic constituents are under suspicion as well, both for man and mice, and are being tested in mice. My results also support to some extent the irritant theory of cancer, the irritation or stimulation or disturbance of the cells being due to the continual presence and addition of a particular dust. Thus constant activity is required on the part of the phagocytes and lymphatics of the lung. There is otherwise no inflammatory reaction. A cause of cancer may be prolonged irritation without inflammation.

Certain statistics for human lung cancer support my findings for mice and I do not understand why Valade should conclude that my results for mice cannot be applied to man merely because, as he states, he could not produce cancer of the lung in 50 rats by intratracheal injections of methylcholanthrene; moreover in some cases sarcoma of the trachea was produced. With other technique the result might be different and tumours be produced in the lung as well. Valade does not mention Möller's research (2423) wherein he obtained cancer of the lung of rats by tar-painting. So far as I know, it was only a year later that the same results was established for mice (Murphy and Sturm (2520)). This does not support Valade's statement that it is easier to produce lung tumours in mice than in rats or other animals. I have concluded other experiments with mice using other different dusts and soot, and I do not always find it easy to increase experimentally the incidence of lung tumours in any strain of mice. These result add weight to the more positive results with road dust: they will be published shortly." (pages 603-604 of ref. 3954)

The above letter explained one of several reasons why American scientists emphasized selection of mouse strains for experimental pulmonary carcinogenesis. The debate on relevance of animal experiments to human cancer continued up to the present, although recent exponents of "Valade" have become less vocal.

British and other laboratories. With the exception of Watson and his colleagues from the University at Sheffield who studied skin tar tumors in rats (3334) and mice (3041), the other investigators used only mice. Twort & Twort from Manchester University, tested over a hundred samples of mineral oils including shale oils, petroleum oils, and mixtures. They reported that potency measured by skin painting response was related to intensity of fluorescence (3130, 3454). Mottram from the London Radium Institute, reported that precancerous lesions induced by benzpyrene became malignant as a result of irradiation (3546, 3762, 3859). Castration did not influence susceptibility of mice to sarcoma cause by subcutaneous injection of methylcholanthrene (3744). Mouse exposure to air-borne dust was being studied at the University of Birmingham and results were not available during the 1930's (3860).

American Research on Experimental Carcinogenesis.

In the United States, the emphasis in experimental cancer research was on the selection of an appropriate animal model. All available publications during the 1930's were on mice subjected to either inhalation of coal tar or to injection of a potent carcinogen previously studied by mouse skin painting. Seelig and Benignus from the Barnard Free Skin and Cancer Hospital at St. Louis, exposed mice to soot by mixing the powder with the bedding of cages (3648, 3861, 3862). The Bar Harbor black strain mice known to be resistant to lung tumors, had a spontaneous incidence of less than 1 percent. A 10 percent mixture of gas-work tar in lampblack failed to induce lung tumor in contrast to the positive results from exposure to chimney soot. Unfortunately a

susceptible strain was used in the latter experiment so that the testing results could not be compared.

Shimkin, from Wolcott Gibbs Memorial Laboratory at Harvard University, used intratracheal administration of hydrocarbons. About 90 percent of Strain A mice developed lung tumors within four months after the intratracheal injection of 0.1 mg. of 1,2,5,6-dibenzanthracene or methylcholanthrene dispersed in 0.1 cc. horse serum and cholesterol. However, since the procedure alone caused 35 percent mortality, the intratracheal administration was discarded in favor of intravenous injection (3956).

Andervont & Lorenz, from the USPHS Office of Cancer Investigations at the Harvard Medical School, selected a standard procedure, i.e., subcutaneous injection of 1,2,5,6-dibenzanthracene-lard solution to mice of several strains. From 1935 to 1939, nine articles were published with the following summaries:

> 1. "The presence of lung tumors in mice following the subcutaneous injection of dibenzanthracene-lard solution cannot be explained at this time. Practically all the lung tumors appeared in strain A or stock mice. The only common factor of these mice is their albino coat color. The mice of strain A are of pure stock and show a tendency toward the development of spontaneous tumors, but the ordinary stock mice used in this laboratory rarely develop spontaneous growths. While it is known that mice of strain A do possess a tendency toward the development of lung tumors, routine autopsies of these animals reveal very few such growths. No instance of lung tumor has been found in 100 routine autopsies of the stock mice.
>
> Microscopic examination of lung growths showed that practically all were carcinomas, regardless of whether the mouse had a subcutaneous sarcoma or no tumor at the site of the dibenzanthracene-lard injection. Thus, it may be assumed that the lung growths are primary tumors. The problem concerning lung tumors is receiving further consideration." (pages 1216-1217 of ref. 3548)

> 2. "In these experiments mice of strain A were given subcutaneous injections of a lard-dibenzanthracene solution. It was found that more of these animals developed lung tumors than subcutaneous tumors and, in addition, that the lung tumors arose earlier than did the subcutaneous growths. Hence it would appear

that the lungs of these mice were more delicate test objects than the subcutaneous tissues for the carcinogenic activity of 1,2,5,6-dibenzanthracene.

The reason for the appearance of lung tumors in mice painted with tar or injected with carcinogenic compounds is unknown. The observations recorded in this paper indicate that in strain A mice the lung response occurred in a relatively short period of time. While it does not appear likely that 0.8 mg of 1,2,5,6-dibenzanthracene in 0.2 cc of lard was capable of altering the body state of mice to such an extent that lung tumors arose so much earlier than under normal conditions, it is not impossible that very small amounts of a carcinogenic agent left the site of injection and came into contact with the tissues of an organ which are known to be extremely susceptible to tumor growth." (page 220 of ref. 3745)

3. In this experiment 21 females of strain A were bred to males of strain C 57 black, and 21 females of strain C 57 black were bred to males of strain A. The mice of strain A are known to be susceptible to both spontaneous and induced lung tumors, while the mice of strain C 57 black are known to be very resistant to the development of all spontaneous growths, and in this laboratory no lung tumors have thus far been induced in them by the subcutaneous injection of a lard-dibenzanthracene solution. The progeny of this mating has been designated as the first hybrid generation. Females ofthe first hybrid generation were mated to the brothers to procure mice designated as of the second hybrid generation.

The absence of lung growths in a high proportion of uninjected controls of both the first and second hybrid generations shows that the lung nodules in the injected mice did not arise spontaneously and, in addition, shows that the lungs of the 62 second generation mice killed on July 23, 1936, were more responsive to the induction of tumors than the subcutaneous tissues, for 43 had multiple lung tumors without any evidence of a subcutaneous growth. This finding is similar to the results obtained in other experiments with strain A mice.

The presence of lung tumors in a high percentage of animals of both the first and second hybrid generations shows that the susceptibility of this organ to tumor formation induced by the subcutaneous injections of a lard-dibenzanthracene solution is inherited in a dominant manner." (pages 313-314 of ref. 3746)

4. "Seven pulmonary tumors arising in strain A mice which had received 1,2,5,6-dibenzanthracene parenterally have undergone from 3 to 23 serial passages in the subcutaneous tissues of normal mice. Three of the tumors consisted of carcinomatous elements mostly in the primary tumor as well as in the earlier passages, and all three have changed into sarcomas in subsequent passages. One other tumor has retained its carcinomatous structure through eight animal passages. It is suggested that the three tumors

exhibiting a change in their histological appearance arose as mixed tumors induced by the direct action of a carcinogenic agent upon both epithelial and connective tissue elements in the lungs." (pages 354-355 of ref. 3747)

5. "Dog-serum and horse-serum dispersions of 1,2,5,6-dibenzanthracene were injected intravenously or subcutaneously and lard solutions of the same compound were injected subcutaneously into pure strain mice. The serum dispersions, when injected intravenously, induced lung and liver tumors, and when injected subcutaneously, produced local tumors at the site of injection as well as lung and liver tumors. Lard dispersion, when injected subcutaneously, evoked local tmors at the injection site and also produced lung and liver tumors.

The appearance of lung and liver tumors in mice injected subcutaneously is evidenced that 1,2,5,6-dibenzanthracene is capable of producing tumors in tissues which are distant from the site of injection." (page 646 of ref. 3748)

6. When 1:2:5:6-dibenzanthracene was adsorbed on charcoal and injected subcutaneously into strain C3H mice, it produced tumors at the injection site. When charcoal was added to a horse-serum dispersion of 1:2:5:6-dibenzanthracene and the resulting mixture injected subcutaneously into strain C3H mice, tumors arose more rapidly at the injection site than in control mice injected subcutaneously with the horse-serum dispersion. Induced lung tumors were found in mice injected with the horse-serum dispersion but such tumors were not observed in mice injected with the horse-serum dispersion to which charcoal had been added. These results suggest that charcoal held the carcinogenic compound at the site of injection. When dibenzanthracene charcoal was injected subcutaneously into strain A mice, it induced tumors at the site of injection in but a few mice, which indicates that the subcutaneous tissues of mice of strain A are more resistant than those of strain C3H to the carciogenic action of dibenzanthracene charcoal. Subcutaneous injection of dibenzanthracene charcoal into strain A mice induced very few, if any, lung tumors which is evidence that the dibenzanthracene was held firmly by the charcoal. This is regarded as further evidence that lung tumors are induced in mice by a direct action of the cacinogenic agent upon the lung tissues." (page 1939 of ref. 3749)

7. "Reciprocal breeding was carried on between mice of strains C3H and I and strains C3H and Y. The female parent mice and most of the hybrid mice were injected subcutaneously with a lard-dibenzanthracene solution. The results of the investigation may be summarized as follows: (1) The C3H female parents were more susceptible to the carcinogen than either the I or Y female parents; (2) The hybrid mice were of intermediate susceptibility when compared with the susceptibility of the parent strains; (3)

Hybrid mice derived by mating strain C3H to strain I were considerably more susceptible to induced pulmonary tumors than those derived by mating strain C3H to strain Y; (4) Female hybrids born to C3H mothers and I fathers were more susceptible to spontaneous mammary cancer than female hybrids born to C3H mothers and Y fathers." (page 1670-1671 of ref. 3863)

8. "Hepatomas occur spontaneously in strain C3H mice. Eighty-five female mice one year of age or older exhibited an incidence of 11.7 percent at an average age of 16.9 months, while 80 males in the same age group had an incidence of 22.5 percent at an average age of 15.1 months. Pulmonary tumors also occur spontaneously in strain C3H mice but their incidence in mice over one year of age (7.2 percent in 165 animals) is lower than the incidence of hepatomas. Primary pulmonary tumors can be induced in strain C3H animals by the subcutaneous or intravenous injection of dibenzanthracene. Injection of the hydrocarbon hastens their appearance and increases their number. Definite conclusions are not justified as to whether hepatomas are induced by dibenzanthracene or methylcholanthrene." (page 1168 of ref. 3957)

9. "Parenteral administration of 1:2:5:6-dibenzanthracene induced pulmonary tumors in mice of strains D, M, C57 brown, and C57 black, and hybrids derived from the D and C57 black strains. These strains are highly resistant to the development of spontaneous pulmonary tumors." (page 1528 of ref. 3958)

Magnus, from St. Bartholomew's Hospital, London, attempted to produce cancer of the stomach by the direct introduction of 1:2:5:6-dibenzanthracene. This was a failure except that lung tumors were produced in a high percentage of animals.

"In a series of market mice with a lung tumour incidence of from 4 to 8 per cent. multiple bronchial papillomata were produced in 95.2 per cent. by the introduction into the stomach of a suspension of 1:2:5:6-dibenzanthracene in olive oil. It is highly probable that aspiration of minute quantities of the carcinogenic agent accounts for the production of these tumours. In 75 per cent. of the affected mice the bronchial papillomata showed clear evidence of malignancy, with metastasis in two mice. The morbid anatomy of spontaneous and of artificially induced lung tumours in mice is the same. Assuming that the material introduced did in fact reach the lungs by aspiration, the smallness of the doses of 1:2:5:6-dibenzanthracene required to produce lung tumours in the mouse is emphasised." (page 30 of ref. 3955)

The above summaries illustrate the extent of research on the most potent polycyclic aromatic hydrocarbon causing lung tumor in mice, regardless of route of administration. It should be recalled that 1:2:5:6-dibenzanthracene was not known to be present in coal tar or tobacco tar. It has remained as a laboratory research chemical substance.

Bittner from the Roscoe B. Jackson Memorial Laboratory, recorded the occurrence of spontaneous lung tumors in A stock mice and reciprocal hybrids between A and C57 black stocks. He concluded that susceptibility to spontaneous pulmonary tumors was probably transmitted by a sigle dominant Mendelian factor (3864). Breast tumor incidence was high in breeding females and low in virgin females. Diet, per se, influenced breast-tumor incidence primarily through the physical condition of mice reaching the cancer age (3549, 3959).

Lynch, from the Rockefeller Institute for Medical Research, continued with studies on tumor susceptibility and heredity. In the fifth publication of the series, she concluded:

> "A male mouse from a strain with a high incidence of spontaneous lung tumors was crossed with several females derived from a low tumor strain. The first generation of offspring were then backcrossed to individuals of the original strains. The resulting two groups of offspring differed significantly in the incidence of spontaneous tumors of the lung. These facts are discussed in relation to others previously dscovered. It seems clear from the evidence presented that there are among mice constitutional types which differ in incidence of tumors of the lung and that the differences are inherited. The number of genetic factors involved has not been determined. No influence of sex was apparent. The possibility of there being genetic factors which affect tumor age will be dealt with later." (pages 759-760 of ref. 3131)

Experimental Carcinogenesis in Rabbits.

There were no application of polycyclic aromatic hydrocarbons to test rabbit lung. There was an abstract indicating that coal smoke over a period of 80 days diverted into a chamber caused pulmonary fibrosis but no mention of new growth (3750). Rabbits have been used for study of naphthalene metabolism, which was relevant to the induction of experimental cataract (3455). Papilloma virus was demonstrated to be transmissible from wild cotton tail rabbits to wild and domestic rabbits (3335). The intravenous injection of the virus caused malignant lesions on tarred skin (3647, 3865, 3960). It was not known whether the virus was transmitted from rabbit to rabbit in the process of tarring the ears, without intravenous injection. The carcinogenic effect of papilloma virus was discussed in a 1987 article by Harris in his P81 Exhibit, authored by Flory.

Radiation. The review article by Ewing entitled "Tissue Reactions to Radiation" related to therapeutic application rather than adverse reaction to carcinogenicity (2604). Mice with transplanted sarcoma have been useful in estimating the therapeutic dose of roentgen rays and gamma rays (3451). Full body irradiation of mice resulted in appearance of tumors including lung and breast lesions (3649). Rabbit lung has been used to demonstrate the initial hyperactivity and late death of ciliated cells following radon implantation (3650). There was no experimental basis to support or exclude the possibility that repeated chest x-ray during the 1930's or earlier was a cause of increasing incidence of lung cancer. The occurrence of malignancy in workers of luminous watch dials was well documented (3118). A similar epidemiologic study on population group exposed to chest x-ray was not conducted and reported.

Human relevance of animal skin painting.

The skin painting studies were conducted primarily to detect carcinogenic constituents of coal tar. The therapeutic use of any agent derived from coal products had to pass a safety test. Wood demonstrated that purified mineral oil (liquid petrolatum USP) was not the cause of cancer in skin painted mice (3042, 3123). Human forms of arsenic-epithelioma and keratosis (3550) were difficult to reproduce in mice so that there were exception to the general rule of usefulness of skin painting experiments. The crucial test relating to 3:4-benzpyrene applied to human skin was conducted in 1939, prior to strict regulations of clinical testing. Cottini & Mazzone, from the University of Catania, Italy, reported their results:

> "1. Daily skin applications of a 1 per cent solution of benzpyrene in benzol in 26 human subjects for variable periods, not exceeding four months, resulted in definite manifestations localized to the treated areas. Erythema, pigmentation, desquamation, the formation of verrucae and infiltration developed in chronological order. Pigmentary and verrucous lesions were the most common observed changes. The gross and microscopic characteristics of each stage are described.
> 2. Following the suspension of treatment after a maximum of 120 applications or when evidence of infiltration appeared, the manifestations regressed completely within two to three months. Although reversible and apparently benign, the changes undoubtedly represented early stages of a process which would have ultimately gone on to neoplastic proliferation. In a broad sense they may be designated as prototypes of a precancerous process.
> 3. The alterations were more pronounced in older than in younger individuals, and on the unprotected skin surfaces. The reaction of young patients with active gummatous lesions was comparable to that observed in the older group.
> 4. In patients with pemphigus vulgaris benzpyrene produced a bullous eruption comparable in appearance and course to the spontaneous disease. The protected and unprotected skin of a patient with xeroderma pigmentosum, while extraordinarily sensitive to ultraviolet irradiation, did not react characteristically to benzpyrene.
> 5. Treatment with benzpyrene of ulcerated squamous-cell cancer of the skin was followed by temporary amelioration. In one instance an analgesic effect was observed. Limited retardation of

the progress of mycosis fungoides lesions in the tumor stage occurred in one case after local application of benzpyrene. Basal-cell cancer and desquamating lesions of psoriasis or porokeratosis were unaffected.

6. The assumption appears warranted that benzpyrene, if applied to human skin for protracted periods, would be carcinogenic as it is in animals." (pages 194-195 of ref. 3961)

The above conclusion applied only to skin cancer, based on human occurrence simulated by skin painting in experimental animals. However, there has been no reported human experiment of inhaling polycyclic aromatic amines to support the contention that animal exposure can be applied to human cancer. It is possible that in the annals of human experimentation conducted by Nazi physicians, carcinogens were used. This subject is discussed in Chapter IV and Part Four of this review.

E. HOSTAL SUSCEPTIBILITY FACTORS

During the 1930's, although occupational/environmental or extrinsic factors were being investigated extensively, the intrinsic factors influencing susceptibility of host was not being overlooked. The scope of intrinsic factors included heredity, diet and nutrition, acute bronchopulmonary irritation, previous chest trauma, chronic pulmonary dust diseases, and pulmonary infections. Additionally, there were efforts to understand immunologic responses influencing ultimate new growth formation in experimental animals.

Heredity

The most significant development in strengthening the importance of inherited susceptibility was the discovery of mouse strains with lung cancer, either spontaneously or induced by coal tar skin painting (3866). The susceptibility was inherited as a dominant Mendelian gene, based on breeding and crossbreeding of two or more inbred strains (see above under Topic D, Experimental Carcinogenesis.)

According to Warthin, from the University of Michigan Hospital at Ann Arbor, it would take a detailed history of three generations of several families to show cancer proneness that was inherited (3043). He described familial predilection to cancer for the respiratory system in males, and for the breast in females. He noted several families with distinct inheritance of two organ susceptibility that was sex limited. During the 1980's, the oncogene

responsible for lung cancer and breast cancer was reported to be in the same chromosome (see page 23).

Lung cancer in children was regarded by some experts as a form of inheritable congenital anlage that became malignant as a result of lung infection (3415, 3763). There were racial differences: Jews in New York City had higher incidence than Gentiles for lung cancer (3302), but lower incidence for cervical cancer (3456). There were differences between white and negro races in relative incidence of malignant diseases and metastasis at death (2733, 2841), but the series reported during the 1930's were limited in number to be meaningful.

The "constitutional factor in cancer" separately from the "irritational" agents that produced neoplastic growth, was announced during the 1926 International Conference on Cancer at Lake Mohawk. In an Editorial for the Bulletin for the Control of Cancer, Little re-emphasized the importance of constitutional factor which determined the tendencies towards or against the formation of cancer (3651). The susceptibility was "passed from one generation to another as part of the natural biological characteristics of the individual. If the constitutional factor was not present, there might conceivably be hyperplasia or even the formation of benign tumors, but the cancerous change would theoretically not be possible." The theory was "most promising" during the 1930's and supportive evidence became available during the next three decades.

Diet and Nutrition

Hoffman wrote a monograph on Cancer and Diet relating to the disease in general (3701). There was no section devoted to lung cancer although relevant information was scatterred throughout the book. Hueper's unpublished study on the influence of sulfur-containing compounds were discussed on pages 271 and 641 of Hoffman's monograph. The manuscript was characterized as "the best exposition of the problem yet presented in the subject of sulfhydryl compounds."

The manuscript was later published by Hueper and two articles are appended (3311, 3449). The articles indicated that Hueper was at the Cancer Research Laboratories of the University of Pennsylvania, prior to working for the Haskell Laboratory of Industrial Toxicology at DuPont. Hueper's views on lung cancer (2623, 2933) were not discussed in Hoffman's monograph (3701) and Hoffman's article on smoking and cancer (3131).

Little wrote an Editorial on the subject of "Diet and Cancer." The relevant paragraphs on possible relationship were:

> "The experimental work which has been done with laboratory mammals has repeatedly shown that different strains of mice kept on the same diet may exhibit a widely divergent incidence of cancer. Obviously, in these cases, great differences in cancer incidence depend upon factors other than a diet which has been standardized in so far as possible.
>
> It is also well to remember that any problem of diet has several very definite phases. In the first place there is to be considered the actual amount of various food elements taken into the stomach. This is one variable. In the second place there is to be considered the physiological age and function of the various time elements in the digestive tract. This provides another variable. The third variable is the amount and rate of absorption of various food elements - a process which is the result of the interaction of the two factors already mentioned. There then follows a fourth factor, namely what the body does with the nutritive elements absorbed. The whole question of storage, metabolism, elimination of waste products and other highly involved processes enter into the situation.

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> It does not take a great deal of technical training to see how complicated the whole problem of diet actually is. To prove a direct and simple relationship between any element in the diet and the incidence of a malignant tumor is no easy matter. The number of carefully planned and scientifically controlled experiments in this field is surprisingly small. The amount of ill-conceived and loosely conducted investigation is discouragingly large.
>
> There is little prospect that the amount of the latter type of work can be diminished. People enjoy obtaining 'definite' results even though careful analysis reveals the inaccuracy of their findings.
>
> On the other hand, there is no reason why - with the availability of stocks of animals of known genetic constitution - steps should not be taken to establish valid evidence concerning the possible role of different dietary elements in the etiology of cancer. Such experimentation will, of necessity, be slow and tedious. (pages 9-10 of ref. 3652)

Little subsequently contributed to developing mouse strains necessary for meaningful carcinogenesis experiments, an accomplishment that can be regarded as largely an American contribution at a time when European and Latin-American scientists were already satisfied with their own experimental animals. Passey and his collaborators demonstrated in rats that vitamin A caused bronchial metaplasia (3644).

Acute Bronchopulmonary Irritation

The concept that bronchogenic carcinoma was preceded by pathologic or excessive regeneration as a result of acute injury to the airways originated from histopathologic studies. Bogen was among the earliest American investigator who characterized tobacco smoke as an "irritant" (3653). Fried popularized the concept (2935) and other physicians interested on lung cancer endorsed the importance of acute irritation (3013, 3235, 3531). The concentration of a chemical irritant must be low enough to exert cellular death with minimal effect on surrounding tissue to permit cellular regeneration. In cancer-prone

individuals, regeneration was excessive, unlike an individual without the constitutional predisposition. Peller (3756) proposed a theory that irritation by cancer provoking agents led not only to a changed incidence of cancer in the irritated spot, but also to opposite changes in some of the other organs to which they have no relation. He could detect antagonism between cancer incidence between the skin and upper alimentary tract. A similar influence between skin and respiratory system has not been detected nor excluded.

Previous Chest Trauma

Ewing wrote a review article entitled "The Modern Attitude Toward Traumatic Cancer" which contained a section on lung cancer (3511). The appearance was five years prior to the revision of his monograph (4001). The difference was that the review article did not mention tobacco smoke even though Roffo had already published the results of tobacco tar on rabbit skin (see above Topic D). The possibility that Ewing hurriedly added Roffo's observation to page proofs was discussed (page 253). Ewing rejected cases with a record of previous trauma followed by lung cancer, including those cited by Adler (1201). Ewing accepted only one case reported in 1903 by Levine as traumatic in origin. Ewing could not comment on a contemporary report by Jaffe in a cancer patient who had a bullet embedded in the lung (3516). Fried, like Ewing was "sceptical of any etiologic relationship between single traumatic insults and cancer of the viscera" (3201). On the other hand, Behan wrote a monograph on Relation of Trauma to New Growths which was less critical of traumatic etiology of cancer (3901).

Chronic Dust Diseases of Lungs

The fundamental question during the 1930's was whether exposure to occupational dust caused lung cancer. There was no question that fibrotic reactions resulted from inhalation of free silica or quartz (silicosis), coal dust (pneumoconiosis) and asbestos fibers (asbestosis). One proposed theory stated that inhaled dust was not a direct carcinogen but the tissue response in turn led to new growth, provided the individual had the "constitutional" factor of predisposition (3552, 3751, 3752, 3753). There was no information on smoking habits of workers who developed chronic lung diseases. The case reports of lung cancer patients exposed to occupational dusts and with known smoking habits are tabulated above under Topic B (page 180).

Radium miners. Since the turn of the century, miners in Joachimstal, Czechoslovakia, have had a high percentage of malignancies (53 percent) among their deaths. There was a considerable increase cancer mortality rate due to "an enormous frequency of pulmonary cancers in the age period of 35 to 54; an exceptionally high proportion of primary lung cancers, a reduced incidence of cancer in non-respiratory organs; an increased mortality from cancers other than cancer in the younger age groups (3962). It was the conclusion of Pirchan & Sikl (3236) and of Peller (3962) that the lung cancer was caused by radium emanation contained in the air of Joachimstal pits. Ventilation had reduced the radon concentration but there was no immediate reduction in lung cancer incidence because of long latent period of 10 to 20 years (3764).

Miners with silicosis. The coverage on silicosis in Ewing's monograph (4001) illustrated his tendency to favor one group and ignore conflicting opinions. As stated earlier, Ewing did not conduct any original research on

lung cancer, and contents of his monograph represented his favored hypothesis derived from the literature. He favored the concept that "silicosis exhibits no definite tendency to produce cancer in the lung", favoring Lanza (3806), Lynch & Smith (3555), Vorwald & Karr (3869). There were anonymous articles (3817, 3828), and other signed articles (3336, 3759) that excluded or omitted the possibility that silicosis was a probable cause of cancer. On the other hand there were publications from Pennsylvania (3452, 3722), New Jersey (3529), Canada (3237, 3963) and England (3336, 3436, 3832, 3965) that endorsed the concept that silica caused carcinoma. Any influence of miners, mining company and government agencies on the medical publications has been difficult to prove or disprove. It has been difficult to obtain workers' compensation for lung cancer although the federal law permitted compensation for pneumoconiosis in the 1970's.

Asbestosis. Harris cited Lynch and Smith's article entitled "Pulmonary Asbestosis" in his written reply to the question: "Are there any of these diseases for the period covered by your report that was more evidence of an association of cigarette smoking than in the case of lung cancer?" (page 50, ERR). There was no mention of smoking in the cited article of Lynch & Smith (3555) nor in a later article by the same authors (3964). They were among early investigators who reported that some asbestosis patients, because of irritation and metaplasia, may also develop lung carcinoma.

The above authors were from the Medical College of South Carolina. Two other pathologists reported case reports of asbestosis with lung carcinoma: Egbert & Geigen from Yale University School of Medicine (3638), and Gloyne from London Hospital for Diseases of the Heart and Lungs (3238, 3556, 3641). There

was no information on cigarette smoking habits. Most European physicians raised the possibility that asbestos fiber was the carcinogenic agent.

Pulmonary Tuberculosis

Although Ewing stated in his earlier monograph that tuberculosis was a significant etiologic factor in bronchogenic carcinoma (2801), other investigators continued to discuss case reports with both diseases. The only available article on the subject of tobacco causing tuberculosis was by Bogen from Olive View, California (3754) and this was cited by Harris in support of his statement that "although at one time tobacco was ascribed a role in the causation of tuberculosis, such an hypothesis was not seriously enterntained by the late 1930s" (SOA 7.9). Bogen's article had no references and raised questions that remained unanswered because of the advent of chemotherapy.

Fried, another monographer, expressed his opinion that was contrary to that of Ewing's. He reported 13 cases of combined tuberculosis and lung carcinoma. He proposed that the process of "cancerization" of a cavity was analogous to "epithelization" of tuberculous cavity (3547, 3551). Similar case reports were published from clinicians in New York (3021, 3620) and other Northeastern States (3325, 3615, 3829), Midwestern States (1919), and England (2530, 3337). Tuberculosis has been reported to occur with silicosis so that differential diagnosis of the superimposed bronchogenic carcinoma became complex (3457).

Hueper reviewed the controversies whether cancer favored the development of tuberculosis, or vice versa, or antagonism between both. After recounting the literature, he concluded that "the doctrine of antagonism between active

tuberculosis and cancer is supported by numerous and reliable experimental and statistical data and pros by far more evidence in its favor than any other conception of this matter" (3045). Since Hueper is my personal choice for a posthumous expert witness, I favor his opinion instead of Ewing, Fried, and Bogen.

Several case reports were published indicating that influenza preceded the appearance of lung cancer. Since a causal relationship was disproven three decades later, a further discussion of influenza as a predisposing disease is dropped during the next two decades.

Environmental and Hostal Interactions

Hueper and other investigators reported results of animal experiments that related to interactions between carcinogenic substance and the hostal responses leading to new growth in general. Hueper compared allergic and neoplastic disorders and introduced the concept that urinary bladder tumor formation was a form of chemical allergy, and that tumor-bearing animals showed vasclo-connective tissue changes following injection of bacterial Schwartzman active substances (3639). Hueper also described immunologic aspects of leukemia (3231, 3448).

The immunological aspects of heterologous transplantation of human and other mamallian tumors were reported by Greene (3854). Decades later, the introduction of drugs with immuno-suppressive and anti-tumor effects was possible as an indirect outcome of these developments in the laboratory.

Several studies were described relating to cellular responses of lung tissue that directly or indirectly led to new growth: influenza virus in mice

(3755), subcutaneous injections of asbestos fibers in rabbits (3046), intrapleural injections of electrolytes in rabbits (2842, 3044), vitamin A deficienty in rat (3644), inhalation of silicon carbide dust in guinea pigs (2843, 2844), intratracheal injection of silica in rabbits (3239, 3757, 3758), and metabolism of polycyclic aromatic hydrocarbons in rabbits (3455) and dogs (3554, 3760). Although human observations suggested that dyspituitarism was the probable cause of clubbing of fingers in patients with lung cancer (3240), the syndrome could not be reproduced in experimental animals.

The influence of trauma on initiation of tumor and on site of metastases were studied in experimental animals (1414, 2956). By reducing oxygen content of blood, inhalation of carbon monoxde caused a marked retardation on rate of growth of mouse carcinoma (3241). Kreyberg described dietary influences on mice with tar skin cancer (3858) and additional details are reported in the next chapter (IV).

In later decades, the subject of environment-host interactions was extensively studied. It was a subject that appealed for a cooperative effort among clinicians, biologists, chemists, biochemists, experimental pathologists, immunologists and epidemiologists. I have selected progress in environment-host interaction research as the connecting link among chapters.

F. THEORIES OF PULMONARY CARCINOGENESIS

The theories of causation of cancer during the 1930's are essentially an extention of those discussed in earlier decades (see Chapter I and Chapter II). There is additional support for tobacco smoking, occupational/environmental factors and hostal susceptibility. The similarities and differences between the two extrinsic groups (tobacco smoking and occupational/environmental factors) are summarized below. This is followed be revisions in Harris' summary statements that continue through Chapter IV, thus completing the literature review prior to 1950. The literature for the 1940's is entitled "The Postwar Publication Explosion on Pulmonary Carcinogenesis" which was selected after collection and grouping of copies of literature. Since the entire literature before 1950 and 1950 to 1966 exceed 3000 articles that relate to pulmonary carcinogenesis, the development of a subject index has been attempted repeatedly for the past six months. The final product called Etiologic Topical Index has been tested and applied to over 600 bibliographic references for the 1930's.

Similarities and Differences Between Tobacco Smoking and Occupational/ Environmental Factors.

By reviewing the literature decade by decade, it has become apparent that by the end of the 1930's, occupational/environmental factors were more widely accepted than tobacco smoking as the extrinsic "irritant" leading to lung cancer. The emphasis in the selection of literature was to illustrate Harris'

shortcoming such as omission of additional references by the same authors, overlooking the considerable amount of human and experimental animal studies relating to occupational/environmental causes of lung cancer, and assuming that European, Japanese and Latin American research studies on tobacco smoking were credible enough to American scientists who could not ignore the political events between the first and second World Wars. The highlights of similarities and differences between tobacco smoking and occupational/environmental factors are separated according to subtopic headings: lung cancer monographers; lung cancer morbidity and mortality; and experimental carcinogenesis.

Lung cancer monographers. Over twenty monographers devoted to human lung cancer were overlooked by Harris who favored Ewing's monograph on all forms of neoplastic diseases. The contents of twenty monographs are compared and I have concluded that there was more detailed discussion on etiology in lung cancer monographs compared to the book by Ewing. All monographers agreed that occupational/environmental factors were generally accepted as the extrinsic "irritant" on the susceptible host. The coverage on tobacco smoking was limited in scope or even omitted in half of lung monographs and review articles. The quotations on the origin of "extrinsic" hypotheses are purposely lengthy because the 1930's marked the decade of acceptance of occupational/ environmental causes of lung cancer.

Moribidty and mortality studies. German scientists preceded other Europeans and Americans in recognizing that coal tar products and combustion emission were responsible for increasing incidence of lung cancer. I have

anticipated the forthcoming events by pooling together the literature on worker exposure and general population exposure to ambient air pollutants, under the heading of occupational/environmental. The increase in exposure of workers and general population was not documented by chemical analysis of ambient air or samples collected from work site because analytical techniques were not yet developed other than simple combustion gases such as carbon monoxide, carbon dioxide, and nitrogen oxides. The techniques for detecting polycyclic aromatic hydrocarbons were being developed in the laboratories during the 1930's and it would take two decades for applying them to field samples.

The causal association between occupational/environmental exposure to the incidence of lung cancer was based on comparative mortality rates of occupational groups in Europe. Reports from the United States were limited to case reports collected in a hospital. There were no case control comparisons because pathologists and clinicians were not yet aware of the necessity. Furthermore, Americans were more concerned with improving antemortem diagnosis and treatment rather than searching and proving the necessity of extrinsic factors. I have the general impression that most clinicians subscribed to the importance of an inherited constitutional predisposition to irritants. Since there were several possible irritants, and predisposition could not be corrected, the only resort was early diagnosis for treatment.

The prevention of lung cancer by discovering that most lung cancer patients were tobacco smokers, was attractive to German and Spanish-speaking scientists numbering about a dozen. They cited each other's scientific accomplishments, including the work of three American laboratories. However, the majority of clinicians overlooked these reports, implicating that tobacco

smoking was a cause of lung cancer which was reflected in secondary citations in the literature of the 1930's. Harris used the tobacco smoking articles, added them to those appearing in the 1940's and formulated his opinion that cigarette manufacturers should have undertaken research relating to lung cancer. But American scientists in general ignored the work of three groups in the United States, and works by German-speaking, Spanish-speaking and Japanese-speaking scientists, probably because of the spread of Nazism, Franco's dictatorship, and Japanese imperialism.

Experimental Carcinogenesis. The most extensive contributions in the understanding of skin cancer were from England and Argentina. Roffo, from Buenos Aires, contributed to the understanding of carcinogenic effects of ultraviolet radiation on the skin. It should be emphasized that mice were used by Roffo for his study of ultraviolet light causing skin cancer. When Roffo initiated his studies on tobacco-associated cancer, he used rabbits instead of mice, and continued observing skin cancer even though lung cancer was the disease supposedly caused by tobacco smoking. His two dozen publications were ignored by most Latin Americans, North Americans and Europeans for the selection of rabbit skin for tests for carcinogenecity, and also because there has been some notoriety in his family name that continued during Peron's regime up to the second return of the Peronistas in Argentina this year. Harris noted less than ten publications that cited Roffo's work on rabbit skin, all of them accepting the applicability of skin cancer studies to lung cancer in humans.

The British laboratories initiated mouse skin painting experiments because of the occurrence of tar skin cancer in humans. The laboratories of Campbell and of Kennaway were very active in identifying carcinogenic cons-

tituents in coal tar. There was no question that the ultimate effect was skin cancer in mice as a result of skin painting. There were also some observations that inhalation or intratracheal injection of coal tar particulates resulted in lung cancer in experimental animals. There were some reports that skin painting of coal tar resulted in lung neoplasm in mice. The conflicting results relating to experimental lung neoplasms are recounted above to serve as a background history of events after the 1930's. The following questions are addressed in the next chapter: Can skin painting experiments relate to pulmonary carcinogenesis? What is the difference in biologic effects and chemical composition of coal tar and "tobacco tar"? What is the significance of the discovery of dibenzanthracene derivative, as the most potent carcinogen, injectable or skin painted, causing lung cancer in susceptible strains of mice? Did scientists use this chemical substance, not present in coal or tobacco tar, as a model for a pulmonary carcinogen administered by dermal, pulmonal, oral, or parenteral injection? How did scientists interested in tobacco and health use this potent carcinogen, either to prove or disprove the causal association of tobacco smoking and lung cancer? I do not know the answers because some of the above questions were not raised in the course of collecting the literature that started October 1988.

Revision of Harris' State of the Art Summary Statements.

I have attempted to revise Harris' statemnts on the basis of literature he has overlooked. Summary Statements under Section 9 of his SOA report reproduced above (pages 136, 137) are revised as follows:

9.1. During the 1930's, there was no reason for manufacturer of cigarettes to conduct or sponsor research into potentially cancer causing effects of its products. The literature on lung cancer, both on animal and human studies, overwhelmingly favored occupational/environmental irritation of susceptible host as the cause. There were a dozen articles proposing tobacco smoke as a cause but they did not meet the standards of acceptability using the model of coal tar causing human and experimental animal cancer.

9.2. The scientific research available by the late 1930's was limited to questionaire survey in three instances. Most other studies on human lung cancer were mortality comparisons of occupational groups that supported the theory that there were chemical irritants in the work environment. The techniques for analysis of components of coal tar were being developed in the 1930's, which were applied to tobacco tar during the next decade. Tobacco smoke was analyzed to the same extent as combustion products containing carbon dioxide, carbon monoxide, aldehydes and alkaloids. There were no animal models for conducting long term inhalational experiments for research on lung cancer of animals exposed to suspected human carcinogens such as dust particles containing coal dust, silica and asbestos fibers. Intratracheal injections of coal tar particles caused lung cancer in experimental animals but similar injection of "tobacco tar" was not equally successful.

9.3. Statements on cancer research support is reviewed in Chapter IV.

9.4. During the late 1930's, and through the early 1940's discussed in Chapter IV, the "scientific evidence that cigarette smoking caused cancer" was minimal and largely from German, Spanish and Japanese researchers. Since Americans were against Nazism, Franco's civil conflict in Spain, and Japanese

imperialism, the evidence was not credible. Warning to consumers was not necessary because other consumer products (like coffee), with known cardiotixic properties, did not require labeling (see Part IV). Furthermore, consumer products that caused skin cancer (like creosote), did not carry a warning label. The human carcinogenicity of coal tar products was already known since the 18th century, and support by skin cancer in animal experiment were available since the beginning of this century.

9.5. The scientific evidence on "other potentially harmful effects of cigarette smoking" available during the 1930's and up to 1942, was not of a nature to require warning to consumers. Additional reasons are discussed in Chapter IV.

9.6 and 9.7. These are reviewed in Chapter IV.

Guidance Needed For Remainder of Project.

I need advise on how detailed or shortened the remaining Chapters should be. The quotations in this Chapter devoted to the 1930's are intentionally lengthy because these articles, widely quoted during the next three decades, and by Harris, are in foreign languages. Furthermore, the conflicts were largely between authorities expressing opinions, counter-opinions and cross-opinions. Most opinions were interpretations of facts that were more abundant for occupational/environmental factors than for tobacco smoking.

I am aware that until the 1980's, there is "no positive proof that cigarette smoking is the most significant cause of lung cancer." The literature prior to 1950 is abundant on occupational/environmental factors, more so than tobacco smoking but the situation was slowly reversed between 1950 and 1966.

Am I to continue to follow all important hypothesis in addition to tobacco smoking, such as: occupational/environmental exposure to fossil fuel products, combustion emission, industrial emission, dust emitted during mining, farming, and indoor occupations; and factors influencing hostal susceptibility such as heredity, constitutional hypothesis, diet and nutrition, previous chest trauma, pulmonary infections and chronic dust diseases of the lung? Am I to concentrate only on statements that are still valid after 1966 and ignore those that were proven to be untrue after 1966 because of availability of new research studies? Shall I stop using lengthy quotations and follow Harris' style of selected sentences to support summary statements? Shall I substitute the use of an Etiologic Topical Index, or a further improvement of it, and simply present articles in a logical sequence of gradation of importance?

A prompt answer to the above questions will be appreciated for work on this project will be put into low gear until such answers are received. I might remind Ms. Thompson and her associates that the scope of this review has not been covered in any monograph published before or since 1966.

Etiologic Topical Index.

While examining the more than 600 articles for this chapter, the necessity to formulate an etiologic topical code became urgent. The overwhelming purpose of the literature search is to compare the role of (a) tobacco smoking, (b) occupational/environmental factors, and (c) hostal susceptibility factors, with special reference to their interactions in pulmonary carcinogenesis. The topical code must also signify the source of information, such as literature review, human studies, and animal studies. It is also

essential that the topical code should be simple enough to determine whether the article supports the tobacco smoking hypothesis, or other causes of lung cancer.

With our limited computer facility, indexing by word was out of the question; instead, an alpha numerical system evolved consisting of a letter followed by a three digits starting with A111 to Z999 and 000 to mean no etiologic information. Alpha (A to Z) represents the general form and subject of the publication. Alpha is followed by a numeric three-digit as information rating: 2nd position _0__ for tobacco smoking; 3rd position __0_ for occupational/environmental; and 4th position for ___0 for hostal susceptibility. Numeric 0 means no information; levels 1 to 4 mean various levels of support for the tobacco smoking hypothesis but against occupational/ environmental and hostal susceptibility; and level 5 means available informa- tion does not permit a lower or higher rating but will be altered at a later date; levels 6 to 9 mean that the article contains information that is <u>against</u> tobacco smoking hypothesis and that occupational/environmental factors and hostal susceptibility are the <u>more important etiologic factors</u>. Publications with ratings of 1 to 4 for all three positions contain information supporting claims of Harris and plaintiffs that cigarette smoking is a significant cause of lung cancer, and its etiologic role is <u>more important</u> than occupational/environmental factors and hostal susceptibility. On the other hand, publications with ratings of 6 to 9 contain information helpful to the tobacco industry, that tobacco smoking as a cause of lung cancer has not been proven to the extent that known pulmonary carcinogens (dibenzanthracene derivatives BCME, creosote) have been positively demonostrated. Such a statement is unlikely to appear

in the open literature but the published information suggest the relative importance of tobacco smoking compared to occupational/environmental factors and hostal susceptibility. Rating 6 to 9 signify that tobacco smoking is not as important as occupational/environmental and hostal susceptibility.

The three numbers should be regarded as relative ratings of tobacco smoking compared to non-tobacco etiologic factors. The specific meaning of the alpha numeric symbols is as follows:

Form and Subject:

Tobacco constituents and lung cancer

- A___ Animal inhalation and intratracheal injection
- B___ Biologic effects other than specific procedures (A, C to F)
- C___ Chemistry of tobacco leaf, tobacco smoke and cigarette manufacture
- D___ Dermal and oral injection of tobacco tar (animal)
- E___ Coal tar and constituents: skin, oral, injection (animal)
- F___ In vitro testing
- G___ Case reports
- H___ Case reports with controls; retrospective
- I___ Prospective studies
- J___ Morbidity studies; other forms of smoking associated diseases
- K___ Mortality studies; other forms of cancer

Occupational/environmental: animal and human studies.

- L___ Coal tar products (except animals under E)
- M___ Vehicular emissions
- N___ Occupation exposure
- O___ Industrial emissions (air, water, food, contaminants)
- P___ Polycyclic aromatic hydrocarbons
- Q___ Suspected carcinogens (radiation, metals, nitrosamines)

Hostal Predisposition

- R___ Heredity (constitutional hypothesis, animal breeding)
- S___ Diet and nutrition
- T___ Pre-existing diseases (tuberculosis, viral, trauma)
- U___ Dust diseases
- V___ Host-environment-tumorinteractions

Special Publications

- W___ Bibliography, Congressional Hearing, Special Society Report
- X___ "Reserved"
- Y___ Editorial, Letter to Editor, news items
- Z___ Monograph, review article, symposium

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Numerical Ratings

Tobacco Smoking (TS)	Occupatioal/ Environmental (OE)	Host Susceptibility (HS)
1 = overall TS > OE, HS	1 = overall OE < TS	1 = overall HS < TS
2 = human TS > OE, HS	2 = human OE < TS	2 = human HS < TS
3 = animal TS > OE, HS	3 = animal OE < TS	3 = animal HS < TS
4 = opinion TS > OE, HS	4 = opinion OE < TS	4 = opinion HS < TS
5 = Uncertain	5 = Uncertain	5 = Uncertain
6 = opinion TS < OE, HS	6 = opinion OE > TS	6 = opinion HS > TS
7 = animal TS < OE, HS	7 = animal OE > TS	7 = animal HS > TS
8 = human TS < OE, HS	8 = human OE > TS	8 = human HS > TS
9 = overall TS < OE, HS	9 = overall OE > TS	9 = overall HS > TS
0 = no information	0 = no information	0 = no information

Examples of the rating system:
111 = tobacco smoking is significant, or more important, cause of lung cancer than occupational/environmental factors and hostal susceptibility.
999 = tobacco smoking is not, or less important, than occupational/ environmental and hostal susceptibility

Application of Topical Index. The above alpha numeric system of indexing is being applied to the literature of the 1930's. Theoretically, there are 25 alphabetical topics (X is reserved) and 1000 ratings for published information, a total of 25000 possible combinations of this alpha numeric system. The rating number must be used with the title of publication and authors because details of animal species, statistical analysis, population groups, chemical procedures, experimental protocol, are not included in the alpha numeric indexing system. The system will serve only one purpose: to identify articles that support the position that tobacco smoking is not, or is not as important cause of lung cancer, compared to occupational/environmental and hostal susceptibility factors, and vice versa. The application of Etiologic Topical Index to Harris' selected scientific articles and to articles that I have collected will be forwarded upon receipt of a new computer promised by mid-June, and the subsequent programing and entry of data in it.

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PART TWO: CHAPTER III - THE 1930's

Note: The four-digit numerical system was described in the Bibliography of Part One (page 18). The 3000 series include publications from 1930 to 1939: thus, 3000's were published in 1930, 3100's in 1931, 3200's in 1932, 3300's in 1933, and so on until 3900's in 1939. Symbols used on cited publications are as follows:

DTH = Deposition Transcript Harris; exhibit and pages
ERR = Expert's Response to Requests (for additional information)
TOP = Transcript of Proceedings; exhibit and pages
SOA = Harris' State of the Art
P = Secondary citations in Harris' representative key articles
DMA = Citations in my 1986 Critique to replace mislaid copies
WHM = Articles derived from 1967 Wynder & Hoffman Monograph
SGR = Cancer references in the 1964 Surgeon General's Report
[] = Harris' SOA report, DTH exhibits, and ERR
# = Articles forwarded with earlier chapters (see Cumulative Index)
* = Articles to be submited with later chapters or at end of project
+ = Foreign articles in need of English translation

Entries without brackets "[]" were derived from manual searches of medical indices as explained on page 11.

Color code of slips attached to photocopies:

Blue = Harris' citations
Orange = Hueper's publications
Green = Wynder & Hoffman's references
Cream = Secondary references in Harris' "P" exhibits; SGR references
Yellow = Tobacco monograph references
White = Index Medicus
Buff = ID numbers from New York collection
Pink = IARC references

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Note: There are no biographical datas of other lung cancer monographers quoted in Part Two, Chapter III, the 1930's.

ARKIN, Aaron, physician; b. Lebau, Latvia, Sept. 6, 1888; s. Isaac C. and Lena (Gordon) A.; came to U.S., 1891; B.S., U. Chgo., 1909, M.D., 1912, Ch.D., 1913; M.A., U. Wis., 1910; m. Alice Kauffmann, Nov. 17, 1949. Fellow physiology U. Chgo., 1908; instr. pharmacology U. Wis., 1909; fellow pathology U. Chgo., Rush Med. Coll., 1910-13; prof. pathology, bacteriology W.Va. U. Med. Sch., 1914-22; research asso. U. Vienna, 1922-26; clin. prof. medicine Rush Med. Coll., 1927-58; clin. prof. medicine U. Ill., 1927-28, emeritus prof., 1958-66; attending physician Weiss Meml., Columbus, Michael Reese hosps., Cook County, Mt. Sinai hosps., Chgo.; cons. physician Cook County, Mt. Sinai hosps., Chgo. Recipient L. C. P. Freer medal Rush Med. Coll. Mem. Israel Med. Soc., A.M.A., Am. Physiol. Soc., Am. Assn. Pathology and Bacteriology, Am. Pharmacol. Soc., Am. Heart Assn., Am. Diabetes Assn., A.C.P., Sigma Xi, others. Research, publs. in immunology, pathology, internal medicine. 1st demonstrated spirochaeta pallida in acquired ulcers of bowel, 1905; 1st description of clin. and x-ray findings in double aortic arch in adults, 1926; 1st description of histologically healed end-stage of periarteritis nodosa, 1930; studies of carcinoma of lung with suppression of its relationship to smoking, 1930; research in antibody prodn., chemotherapy, carcinoma of lung, pancreas, acute pancreatitis, periarteritis nodosa. Died Nov. 1, 1966.

EWING, James, Am. pathologist; b. Pitts., Dec. 25, 1866; s. Thomas and Julia R. (Hufnagel) E.; A.B., Amherst Coll., 1888, A.M., 1891; Sc.D., 1923; M.D., Columbia Coll. Phys. and Surg., 1891; Sc.D., U. Pitts., 1911, Amherst, 1923, U. Rochester, 1932, Union U., 1938, LL.D., Kenyon, 1931, Western Res. U., 1932; m. Catherine C. Halsted, June 19, 1900; 3 sons, James Halsted. Tutor histology, Coll. Phys. and Surg., 1893-97, Clark fellow, 1896-99, instr. clin. pathology, 1897-98; prof. pathology Cornell U., 1899-1932, prof. oncology, 1932-43. Charles Mickle fellow, Toronto, 1935; John Scott medalist, Phila., 1937; hon. mem. Phila. Pathol Soc.; Acad Med., Brazil, Swedish Roentgen Soc., Acad. Med. Budapest; mem. Nat. Acad Sciences, Assn. Am. Physicians, Am. Roentgen Ray Soc., Am. Med. Museums Soc., Am. Assn. Pathologists and Bacteriologists, Soc. Exptl. Biology and Medicine, Harvey Soc., Am. Assn. for Cancer Research. Author: Clinical Pathology of Blood, 1900-03, articles on Identity, The Signs of Death, and Sudden Death, in Text-Book of Legal Medicine and Toxicology, 1903; on Blood, etc., in Text-Book of Legal Medicine, 1910; Neoplastic Diseases, 1919-27, 40. Described form of bone sarcoma which usually affects shaft of long bones, classified tumors; experimented with cancer cure using X-ray and radium; pioneer in use of radium treatment. Died N.Y.C., May 16, 1943.

GRAHAM, Everts Ambrose, Am. surgeon; b. Chgo., Ill., Mar. 19, 1883; s. David Wilson and Ida Anspach (Barned) G.; A.B., Princeton, 1904; M.D., Rush Med. Coll., 1907; spl. chem. studies U. Chgo., 1913, 14; many hon. degrees; m. Helen Tredway, Jan. 29, 1916; children—David Tredway, Everts Ambrose. Intern Presbyn. Hosp. Chgo., 1907-08, asst. attending surgeon, 1912-15; asst., also instr. surgery Rush Med. Coll., 1909-15; mem. staff Otho. S. A. Sprague Meml Inst., Rush, Chgo., 1912-15; chief surgeon Park Hosp., Mason City, Ia., 1915-17; prof. surgery Washington U. Sch. of Medicine, 1919-51, emeritus since 1951; surgeon in chief Barnes Hosp., St. Louis Children's Hosp.; surgeon in chief Peter Bent Brigham Hosp., 1925; temp. prof. surgery St. Bartholomew's Hosp., London, 1939. Mem. NRC, 1925-46; mem. Nat. Bd. Med. Examiners, 1924-33 chmn. Am. Bd. Surgery, 1937-41. Recipient others; Gross prize in surgery, 1920; Leonard prize Am. Roentgen-Ray Soc., 1925; Gold medal Am Radiol. Soc, 1925, for devel of cholecystography; Gold medal and certificate of merit St. Louis Med. Soc., 1927; Gold medal So Med. Assn., 1934; John Scott medal City of Phila., 1937; St. Louis Award, 1942; Lister medal Royal Coll. Surgeons, Eng, 1942; Roswell Park medal, 1949; Am. Coll Chest Physician medal, 1949, Miss. Valley Med. Soc. medal, 1949; distinguished service medal A M.A., 1950; Bigelow medal Boston Surg Soc., 1951, Charles Mickle Fellowship, Univ., Toronto, 1943. Fellow A.C.S. (pres); mem. A M A., Am. Assn. Thoracic Surgery (pres.), Soc. Clin. Research, Am. Philos Soc.; mem., hon. mem. other Am. and fgn med. socs. Author Empyema Thoracis, 1925; Diseases of the Gall-Bladder and Bile Ducts, 1928, also sect. in Medical and Surgical History of World War, 1924. Editor: Surgical Diagnosis, 1930; Yearbook of Surgery, 1926-27. Co-editor Archives of Surgery, 1920-45, Annals of Surgery, 1935-45, editor Jour. Thoracic Surgery, 1931——. Described disturbed mechanics of respiration and circulation when normal intrathoracic pressures are altered, developed (with W. H. Cole) Graham-Cole test, or method for cholecystography, an X-ray visualization of gall-bladder, 1924; devised new treatment for chronic abscess of the lung contbd. to pathology and treatment of carcinoma of bronchus, explanation of particular toxicity of choloroform and similar anaesthetic agts; performed (with J. J. Singer) 1st successful total pneumonectomy, 1933. Died Mar. 4, 1957.

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LITTLE, Clarence C(ook), Am. biologist; b. Brookline, Mass., Oct. 6, 1888; s. James Lovell and Mary Robbins (Revere) L.; A.B., Harvard, 1910; S.M., Grad. Sch. of Applied Science (Harvard), 1912, Sc.D., 1914; LL.D., U. N.H., 1924, Albion (Mich.) Coll., 1925, U. N.M., 1929, Colby College, Waterville, Me., 1935; Litt.D., U. Me., 1932; Sc.D., U. Chgo., 1950, Boston U., 1951; L.H.D., Dickinson Coll., 1951; Ed.D., Marietta Coll., 1952; m. Katharine Day Andrews, May 27, 1911 (div. 1929); children—Edward Revere, Louise, Robert Andrews; m. 2d, Beatrice W. Johnson, 1930; children—Richard Warren, Laura Revere. Sec. to Corp. Harvard Univ., 1910-12; research asst. in genetics, 1911-13, research fel. in genetics (cancer commn.), 1913-17, asst. dean, 1916-17, overseer, 1942-48, 1955-61, all Harvard U.; faculty Harvard Med. Sch., 1917-25; asst. dir., Sta. for Exptl. Evolution, Carnegie Instn., 1921-22; pres. U. Me., 1922-25, U. Mich., 1925-29; dir. Jackson Meml. Lab., 1929-56, dir. emeritus, 1956—. Dir. Am. Cancer Soc., 1929-45. Sci. dir. Council for Tobacco Research, 1954—; mem. sci. adv. bd., Gesell Inst Child Devel. 1952—. Officer, del., or mem. several confs. eugenics, euthanasia, birth control, genetics, 1921—. Recipient medal Am. Cancer Soc., 1950, Pioneers Hall of Fame, 1952. Fellow Nat. Acad Scis., Am. Acad. Arts and Scis., N.Y. Acad. Medicine, A.A.A.S., Nat. Inst. Social Scis; mem. nat., state, tech., scientific and profl socs. and orgns, officer or dir. several. Author: Civilization Against Cancer, 1939; Genetics, Biological Individuality, and Cancer, 1954; Inheritance of Coat Color in Dogs, 1956; Research and pubis on genetics, cancer research, edn. and social problems. Address: Ellsworth, Me.*

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J. SINGER, Jacob Aaron, physician; b. Lords, Eng., July 12, 1885; s. Abraham and Rebecca (Silverblatt) S.; came to U. S., 1885; M.D., Washington U., 1904; interne, 1904-06, specialized in Tb thereafter; med. dir. Los Angeles Sanitarium; asso. clin. prof. medicine Washington U.; also U. So. Cal.; cons. Diseases of Chest, Cedars of Lebanon Hosp., Los Angeles, Barnes Hosp., Jewish Women's Hosp., Childrens' Hosp., U. S. Mariner' Hosp. Mem. or fellow Am. Assn. Thoracic Surgeons, Am. Coll. Chest Physicians, A.M.A., Central Soc. Clin. Research. Author: (with Everts Graham and Harry Bullen) Surgical Diseases of the Chest, 1935; also papers on surg. and med. treatment of pulmonary Tb. Pioneer in surg. treatment of pulmonary Tb, especially in use of artificial pneumothorax; successfully removed (with E. A. Graham) entire lung for carcinoma of bronchus, circa 1933. Died Apr. 13, 1954.

TRUHAUT, René, French toxicologist; b. Pontenx-les-Forges, May 23, 1909; s. Jules Alexis and Sidonie (Lucas) T.; D. Pharmacy, Faculty Pharmacie and Sciences, U. Paris, 1947, D.Sc., 1952; Lab. chief Curie Inst., Villejuif, Cancer Inst., 1941-48; asso. prof. Faculty Pharmacy, Paris, 1948-55, titular prof. toxicology and hosp. hygiene, 1955-80, Expert for food additives and pesticides WHO, 1955—; expert for toxic substances in industry ILO, Labor orgn., 1959—. Decorated Légion d'Honneur. Mem. Internat. Union Pure and Applied Chemistry, Societe Espan. soc., 1961—), Internat. Union Contra Cancrum (past chmn. com. on causative factors cancer). Research, numerous publs. on chem. carcinogenesis, chemotherapy of cancer, toxicology of thallium, fluorine, arsenic, lead, mercury, cadmium, food. solvents, food additives, pesticides; contributed to establishment of methodology for toxicological evaluation of these chemicals for the purpose of establishing acceptable daily intakes and tolerances; biochem. orientation of toxicological research. Home: Ville-Evrad, 2, rue Jean-Jaurès, 93-Neuilly S/Marne, France. Office: 4 Avenue de l'Observatoire, Paris, France.

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